
Good ANDA Submission Practices Guidance for Industry

DRAFT GUIDANCE

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For questions regarding this draft document, contact (CDER) Lisa Bercu at 240-402-6902.

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

**January 2018
Generics**

Good ANDA Submission Practices Guidance for Industry

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Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
<https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>

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**Good ANDA Submission Practices
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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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 is intended to assist applicants preparing to submit to FDA abbreviated new drug applications (ANDAs). This guidance highlights common, recurring deficiencies that may lead to a delay in the approval of an ANDA. It also makes recommendations to applicants on how to avoid these deficiencies with the goal of minimizing the number of review cycles necessary for approval.

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

The Generic Drug User Fee Amendments (GDUFA I)² was signed into law on July 9, 2012. Based on an agreement negotiated by FDA and industry,³ GDUFA I was designed to increase the likelihood that American consumers have timely access to low cost, safe, effective, and high-quality generic drugs and to improve the predictability of the ANDA review process. Under GDUFA I, FDA constructed a modern generic drug program that resulted in a significant and sustained increase in communications between FDA and industry, ANDA regulatory actions, and ANDA approvals.

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

² Public Law 112-144.

³ This agreement is reflected in the Generic Drug User Fee Act Program Performance Goals and Procedures letter, available at <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf>.

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39 Despite the advances made under GDUFA I, approximately half of all ANDAs with GDUFA
40 review goals required three or more review cycles to reach approval or tentative approval.⁴
41 Multiple review cycles are highly inefficient, require significant resources from applicants and
42 FDA, and delay timely patient access to more affordable generic drugs.

43
44 Accordingly, after receiving public input, FDA and industry negotiated a revised agreement,
45 reflected in the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal
46 Years 2018-2022 letter (GDUFA II Commitment Letter),⁵ and GDUFA was reauthorized
47 (GDUFA II)⁶ on August 18, 2017. GDUFA II includes important program enhancements that
48 are designed to improve the predictability and transparency of ANDA assessments⁷ and to
49 minimize the number of review cycles necessary for approval. These program enhancements are
50 intended to foster the development of high-quality submissions, ensure the timely resolution of
51 filing reconsideration requests, promote the correction of deficiencies in the current review cycle,
52 and support the development of high-quality resubmissions.

53
54 This guidance has been developed as part of FDA’s “Drug Competition Action Plan,” which, in
55 coordination with the GDUFA⁸ program and other FDA activities, is expected to increase
56 competition in the market for prescription drugs, facilitate entry of high-quality and affordable
57 generic drugs, and improve public health. In conjunction with this guidance, FDA is issuing a
58 *Good ANDA Assessment Practices* Manual of Policies and Procedures, which establishes good
59 ANDA assessment practices for the Office of Generic Drugs and the Office of Pharmaceutical
60 Quality to increase their operational efficiency and effectiveness. This guidance and the Manual
61 of Policies and Procedures are intended to build upon the success of the GDUFA program and to
62 help reduce the number of review cycles for an ANDA to attain approval.

63
64 This guidance describes common, recurring deficiencies identified during FDA’s substantive
65 assessment of an ANDA with respect to (1) patents and exclusivities, (2) labeling, (3) product
66 quality, and (4) bioequivalence (BE).⁹ This guidance also provides recommendations to

⁴ A *tentative approval* is a notification from FDA that an ANDA otherwise meets the requirements for approval under the Federal Food, Drug, and Cosmetic Act (FD&C Act) but cannot be approved until the expiration of a period of patent and/or exclusivity protection; until the expiration of a 30-month stay of approval; or, because of a court order in patent litigation, before a specific date. See 21 CFR 314.3(b) and 314.105(d).

⁵ The GDUFA II Commitment Letter is available at <https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf>.

⁶ Pub. Law 115-52.

⁷ Going forward, the Office of Generic Drugs and the Office of Pharmaceutical Quality will generally use the term *assessment* in place of *review*. *Assessment* means the process of both evaluating and analyzing submitted data and information to determine whether the application meets the requirements for approval and documenting that determination.

⁸ In this guidance, *GDUFA* refers to the generic drug user fee program codified in the Generic Drug User Fee Amendments of 2012 and the Generic Drug User Fee Amendments of 2017.

⁹ The deficiencies and accompanying recommendations in this guidance are organized by FDA’s review disciplines and generally follow the same order as the electronic common technical document. Information on the electronic common technical document format is available at

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67 applicants on how to avoid these deficiencies. FDA comprehensively communicates deficiencies
68 identified during a substantive review¹⁰ of an ANDA in complete response letters.¹¹ Applicants
69 may address the deficiencies identified by FDA by submitting an amendment to their
70 application.¹²

71
72 This guidance does not include a comprehensive list of all of the deficiencies identified during
73 ANDA assessment. In addition, it is each applicant's responsibility to submit a high-quality,
74 complete application that FDA can approve in the first review cycle. FDA strongly encourages
75 applicants to review FDA regulations and all applicable guidances for industry¹³ to understand
76 FDA's current thinking on each topic.

77
78

79 III. PATENT AND EXCLUSIVITY DEFICIENCIES

80

81 The timing of ANDA approval depends on, among other things, the patent and exclusivity
82 protections for the reference listed drug (RLD) on which the applicant relies in seeking approval.
83 An applicant must provide, in its ANDA, information related to any patents listed for the RLD in
84 FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange
85 Book).¹⁴ In particular, an ANDA applicant generally must submit to FDA one of four specified
86 certifications regarding the patents for the RLD under section 505(j)(2)(A)(vii) of the Federal
87 Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)(2)(A)(vii)).

88

<https://www.fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronic submissions/ucm153574.htm>.

¹⁰ Prior to a substantive review, FDA communicates with ANDA applicants that deficiencies were identified during the filing review of their submitted application either through a notification to the applicants (if fewer than 10 minor deficiencies were identified) or in a refuse-to-receive decision. Please see FDA's guidance for industry *ANDA Submissions — Refuse-to-Receive Standards* for additional information on how FDA conveys to applicants deficiencies identified during the filing review and for a non-exhaustive list of deficiencies that may or will lead to a refuse-to-receive determination by FDA. We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

¹¹ It should be noted that the Agency also issues *discipline review letters*, which are defined in the GDUFA II Commitment Letter as "a letter used to convey preliminary thoughts on possible deficiencies found by a discipline reviewer and/or review team for its portion of the pending application at the conclusion of the discipline review." In addition, *information requests* are communications "sent to an applicant during a review to request further information or clarification that is needed or would be helpful to allow completion of the discipline review." GDUFA II Commitment Letter.

¹² For information on amendment classifications and categories, please see FDA's draft guidance for industry *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA*. When final, this guidance will represent FDA's current thinking on this topic.

¹³ Applicants may review the Center for Drug Evaluation and Research's Manuals of Policies and Procedures, which are Federal directives and documentation of internal policies and procedures that are made available to the public at <https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ManualofPoliciesProcedures/default.htm>.

¹⁴ The Orange Book is available at <https://www.accessdata.fda.gov/scripts/cder/ob/>.

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89 If the Orange Book does not list a patent for the RLD that, in the opinion of the ANDA applicant
90 and to the best of its knowledge, claims the RLD or that claims a use of such listed drug for
91 which the applicant is seeking approval,¹⁵ the ANDA applicant must certify that such patent
92 information has not been submitted by the new drug application (NDA) holder for listing in the
93 Orange Book (a paragraph I certification).¹⁶

94

95 With respect to each patent listed in the Orange Book for the RLD, the applicant's patent
96 certification must state one of the following:

97

98 • That such patent has expired (a paragraph II certification)

99

100 • The date on which such patent will expire (a paragraph III certification)

101

102 • That such patent is invalid, unenforceable, or will not be infringed by the manufacture,
103 use, or sale of the new drug for which the application is submitted (a paragraph IV
104 certification)¹⁷

105

106 On or after the date on which FDA has received an ANDA for review,¹⁸ an applicant that has
107 submitted a paragraph IV certification to a listed patent must provide the NDA holder and each
108 patent owner notice of its paragraph IV certification, including a description of the legal and
109 factual basis for the ANDA applicant's assertion that the patent is invalid, unenforceable, or will
110 not be infringed.¹⁹ If a patent is listed at the time an original ANDA is submitted and, in
111 response to a notice of a paragraph IV certification, the NDA holder or patent owner initiates a
112 patent infringement action against the ANDA applicant within 45 days of receiving the required
113 notice, approval of the ANDA generally will be stayed for 30 months from the latter of the date
114 of receipt of the notice by any owner of the patent or the NDA holder or such shorter or longer
115 time as the court might order.²⁰

116

¹⁵ If, in the opinion of the applicant and to the best of its knowledge, there are no patents claiming the RLD that are, or should have been, listed in the Orange Book, the applicant must include in the ANDA a certification in the following form:

In the opinion and to the best knowledge of (name of applicant), there are no patents that claim the listed drug referred to in this ANDA or that claim a use of the listed drug.

21 CFR 314.94(a)(12)(ii).

¹⁶ 21 CFR 314.94(a)(12)(i)(A).

¹⁷ Section 505(j)(2)(A)(vii) of the FD&C Act; see also 21 CFR 314.94(a)(12)(i)(A).

¹⁸ 21 CFR 314.101(b).

¹⁹ Section 505(j)(2)(B) of the FD&C Act. See section III.C of this guidance for more information on notice of a paragraph IV certification.

²⁰ Section 505(j)(5)(B)(iii) of the FD&C Act and 21 CFR 314.107(b)(3)(i). Note that, in some circumstances, the period of the stay may be 7½ years after the date of approval of the RLD rather than 30 months from the date of the notice. See 21 CFR 314.107(b)(3).

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117 The statute provides an incentive and a reward to ANDA applicants that expose themselves to
118 the risk of patent litigation; the statute does so by granting a 180-day period of exclusivity *vis-à-*
119 *vis* certain other ANDA applicants to the applicant that is first to file a substantially complete
120 ANDA that contains, and for which the applicant lawfully maintains, a paragraph IV certification
121 to a listed patent for the RLD (First Applicant).
122

A. Documentation and Notification of a Legal Action Filing

123
124 Applicants that file a paragraph IV patent certification²¹ must subsequently amend their ANDA
125 to provide documentation to FDA regarding (1) their notice of certification that was sent to the
126 patent owner(s) and NDA holder and (2) any legal action that has been taken against the
127 applicant under that paragraph IV notice.²² Specifically, applicants must amend their ANDAs to
128 provide documentation:
129

- 130
- 131 • That their notice of a paragraph IV certification was sent on a date that complies with the
- 132 time frame provided in the regulations for sending this notice
- 133
- 134 • Of the date that this notice was received by the patent owner(s) and NDA holder
- 135

136 This documentation must be submitted to the ANDA within 30 days after the last date on which
137 the notice was received by the patent owner(s) and NDA holder.²³
138

139 Applicants also must submit documentation “within 14 days of the filing of any legal action filed
140 within 45 days of receipt of the notice of paragraph IV certification.”²⁴ Any submission
141 indicating that legal action was initiated against the applicant should include a complete copy of
142 the civil action. If a legal action was not filed by either the patent owner(s) or the exclusive
143 patent licensee within 45 days of its or their receipt of the notice of the paragraph IV
144 certification, applicants should submit an amendment to their ANDA immediately after the 45-
145 day period elapses stating that no legal action was taken by the patent owner(s) and exclusive
146 patent licensee.
147

148 However, applicants have often not submitted to FDA written documentation in a timely fashion:
149

- 150 • Of their timely sending notice of a paragraph IV certification and of the dates that the
- 151 patent owner(s) and NDA holder received notice of a paragraph IV certification
- 152
- 153 • That the patent owner(s) and/or exclusive patent licensee have filed a legal action
- 154

²¹ Paragraph IV patent certifications are described in 21 CFR 314.94(a)(12)(i)(A)(4).

²² 21 CFR 314.95(e) and 21 CFR 314.107(f)(2).

²³ 21 CFR 314.95(e).

²⁴ 21 CFR 314.107(f)(2).

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- That includes a statement that the patent owner(s) and exclusive patent licensee did not file a legal action within 45 days of receipt of the notice of the paragraph IV certification

Applications that lack all required patent/legal documentation or those that do not respond in a timely manner to a request for information may receive a complete response letter.

B. Resolution or Appeal of a Legal Action

If an applicant submitted a paragraph IV certification, litigation is brought against that applicant, and the court enters a decision in favor of the patent owner(s) and/or NDA holder finding the patent valid and infringed, that applicant must notify FDA of the court's decision within 14 days.²⁵

If the applicant appeals the court decision within the time permitted to appeal, the applicant similarly must notify the Agency within 14 days.²⁶ If the applicant does not appeal the court's decision, the applicant must submit an amendment to change its paragraph IV certification to a paragraph III certification; this amendment must certify that the patent will expire on a specific date, or, if applicable, that the applicant is no longer seeking approval for a method of use claimed by the patent.²⁷

Similarly, if the litigation results in a district court decision, a court of appeals mandate, or a settlement order "signed and entered by the . . . district court or court of appeals"²⁸ that specifies that the patent in question is invalid, unenforceable, or not infringed, the ANDA applicant must submit to the ANDA: a copy of the court judgment, written notification of whether or not there is an appeal within the time for appeal, and/or a copy of any order by the court terminating the 30-month or 7½-year stay of approval. If the litigation is resolved with written consent to approval of the ANDA from the patent owner or the exclusive patent licensee, a copy of that written consent must be submitted.²⁹

Timely notification that the court has issued a decision or that the court's decision has been appealed and, when applicable, submission of a timely amendment of the patent certification are necessary for FDA to determine the timing of an ANDA's approval.³⁰

C. Notice of a Paragraph IV Certification

An applicant may not provide notice of a paragraph IV certification that was submitted in an original ANDA to the patent owner(s) and NDA holder until that applicant receives a paragraph

²⁵ 21 CFR 314.107(e)(2).

²⁶ *Id.*

²⁷ 21 CFR 314.94(a)(12)(viii)(A).

²⁸ 21 CFR 314.107(e)(1).

²⁹ *Id.*

³⁰ See 21 CFR 314.107(b)(3).

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192 IV acknowledgement letter from FDA.³¹ Similarly, if an applicant submits an amendment to its
193 ANDA that includes a paragraph IV certification and FDA has not yet informed the applicant
194 that the ANDA was received for review, that applicant must wait to provide notice of its
195 paragraph IV certification to the patent owner(s) and NDA holder until after the applicant has
196 received a formal acknowledgement letter from FDA that the ANDA was received for review.³²
197 The applicant must send notice of the paragraph IV certification contained in the amendment on
198 or after the date it receives acknowledgement from FDA that the ANDA was received for
199 review; this notice must be sent no later than 20 days after the date of acknowledgement from
200 FDA.³³ If FDA has notified the applicant that it has received the ANDA and the ANDA
201 applicant makes a subsequent amendment that requires a paragraph IV certification (see section
202 III.E of this guidance), the notice must be sent at the same time that the amendment is
203 submitted.³⁴

204
205 Notice of a paragraph IV certification that was submitted in an original ANDA or in an
206 amendment before FDA has received the ANDA for review is invalid.³⁵

D. New or Revised Information in the Orange Book

207
208
209
210 If a new patent is listed for the RLD after an applicant submits an ANDA or information related
211 to a patent listed for the RLD is revised³⁶ after an applicant submits an ANDA, that applicant
212 must address these changes to the patent listing for the RLD by submitting an appropriate patent
213 certification or statement for each patent.³⁷ However, applicants have either:

- 214
215 • Provided “serial submissions” of amendments with paragraph IV certifications and sent
216 multiple notices of paragraph IV certifications in anticipation of a newly issued patent
217 being listed in the Orange Book, which is not permissible under FDA’s regulations³⁸ or
218
- 219 • Failed to submit an appropriate patent certification or statement for each newly listed
220 patent or revised patent information
221

³¹ 21 CFR 314.95(b)(2). An *ANDA acknowledgement letter* is the letter that FDA sends when it has determined that the ANDA can be received for review.

³² 21 CFR 314.95(b)(1) and 21 CFR 314.95(d)(2).

³³ *Id.*

³⁴ 21 CFR 314.95(d)(1). Similarly, if the ANDA applicant submits a supplement to an approved ANDA and that supplement requires a paragraph IV certification, its notice must be sent at the same time that the supplement is submitted to FDA. *Id.*

³⁵ 21 CFR 314.95(d)(2).

³⁶ For example, if a new use code is added to the Orange Book for a currently listed patent for the RLD, the applicant must provide an updated paragraph IV certification or statement to FDA to address the newly listed use code.

³⁷ 21 CFR 314.94(a)(12)(i) and 21 CFR 314.94(a)(12)(iii).

³⁸ 81 FR 69610 (Oct. 6, 2016).

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222 An applicant must not submit a paragraph IV certification to the ANDA for a newly listed patent
223 “earlier than the first working day after the day the patent is published in [the Orange Book].”³⁹
224 FDA recommends that applicants monitor the Orange Book and address newly listed patents and
225 revised patents in a timely manner to avoid unnecessary delays to ANDA approval.

226
227 In addition, ANDA applicants have failed to address new exclusivities for the RLD, which may
228 result in a delay in FDA’s approval of an application. FDA recommends that applicants monitor
229 the Orange Book and address exclusivities in a timely manner to avoid unnecessary delays to
230 ANDA approval.

E. Amendments to an Unapproved ANDA

231
232
233 An amendment to an unapproved ANDA must contain either:

- 234
235 • “an appropriate patent certification or statement” or “a recertification for a previously
236 submitted paragraph IV certification” if approval is sought for (1) a new indication or
237 other condition of use, (2) a new strength, (3) an other-than-minor change in product
238 formulation, or (4) a change to the physical form or crystalline structure of the active
239 ingredient or
240 ingredient or
- 241
242 • A verification statement that states that the amendment does not contain one of the those
243 four types of changes⁴⁰
244

245 Applicants, however, have failed to provide either:

- 246
247 • An appropriate patent certification or statement (or recertification) or
248
- 249 • The required verification statement in their amendment to an unapproved ANDA when
250 that amendment did not contain one of the four types of changes described above
251

252 To address this requirement, FDA recommends that applicants provide an appropriate patent
253 certification or statement (or recertification) or, if applicable, include a verification statement
254 (stating, e.g., “This amendment does not contain one of the proposed changes under 21 CFR
255 314.96(d)(1)”) in the cover letter of their amendment to an unapproved ANDA.

F. Notification of Commercial Marketing

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258
259 The 180-day exclusivity period commences upon any First Applicant’s commercial marketing of
260 its drug product (including the commercial marketing by the First Applicant of the RLD or an
261 authorized generic).⁴¹ Under either scenario, a First Applicant must submit correspondence to its

³⁹ 21 CFR 314.94(a)(12)(viii)(C)(1)(ii).

⁴⁰ 21 CFR 314.96(d).

⁴¹ Section 505(j)(5)(B)(iv)(II)(aa) of the FD&C Act and 21 CFR 314.3.

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262 ANDA notifying FDA “within 30 days of the date of its first commercial marketing of its drug
263 product or the reference listed drug.”⁴² If a First Applicant commences marketing of its
264 approved drug product (or the RLD or an authorized generic) and does not notify FDA within
265 this time frame, “the date of first commercial marketing will be deemed [by FDA] to be the date
266 of the drug product’s approval.”⁴³

267
268 To address this requirement and avoid losing the benefit of part of the 180-day exclusivity
269 period, FDA recommends that applicants submit the required notification of commercial
270 marketing to FDA within the 30-day time frame.

271

272

IV. LABELING DEFICIENCIES

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A. Draft Container Labels and Carton Labeling

276

277 Generally, an ANDA’s labeling must be the same as its RLD’s labeling.⁴⁴ There are, however,
278 limited exceptions, including an exception for differences caused by the ANDA and RLD being
279 produced or distributed by different manufacturers.⁴⁵ These differences between the ANDA’s
280 labeling and the RLD’s labeling may include differences (e.g., in the expiration date or in the
281 formulation) that were made to comply with current FDA labeling guidelines or other guidance
282 documents.⁴⁶ FDA reviews ANDA container labels and carton labeling to make certain that
283 differences from the RLD’s labeling do not raise safety concerns.⁴⁷ During this review, FDA
284 considers formatting factors such as the font size, style, and color of the required text; the
285 labeling’s identification of different product strengths; and other methods used to ensure that the
286 required information is presented with adequate prominence.⁴⁸ Applicants sometimes submit
287 draft container labels and carton labeling that do not accurately represent the formatting factors
288 that will be used with the final printed labels and labeling, which makes it challenging for FDA
289 to confirm that the final printed labels and labeling will be adequate.

290

291 To ensure that container labels and carton labeling are adequately evaluated for potential
292 deficiencies, FDA recommends that the draft version of container labels and carton labeling
293 “reflect the content as well as an accurate representation of the layout, text size and style, color,
294 and other formatting factors that will be used with the [final printed labeling].”⁴⁹ In addition, as
295 explained in the FDA guidance for industry *Acceptability of Draft Labeling to Support ANDA*

⁴² 21 CFR 314.107(c)(2).

⁴³ *Id.*

⁴⁴ Section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314.94(a)(8)(iv).

⁴⁵ *Id.*

⁴⁶ 21 CFR 314.94(a)(8)(iv).

⁴⁷ FDA guidance for industry *Acceptability of Draft Labeling to Support ANDA Approval*, at 3.

⁴⁸ *Id.*

⁴⁹ *Id.*

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296 *Approval*, applicants that “receive approval based on draft labeling are responsible for ensuring
297 the content of the [final printed labeling] is identical to the approved labeling.”⁵⁰ Failure to
298 receive this approval may render the product misbranded and an unapproved new drug.⁵¹
299

B. Color Differentiation for Container Labels and Carton Labeling

300
301
302 Factors such as the color and format of container labels and carton labeling can help differentiate
303 multiple strengths within the same product line as well as multiple products within a company’s
304 product line, thereby reducing the likelihood of medication errors. Applicants, however, have
305 submitted container labels and carton labeling for products that lack an adequate differentiation
306 between various strengths and from other drug products.
307

308 FDA recommends that applicants ensure that the color and/or format of container labels and
309 carton labeling is adequately differentiated from other pending and approved products in their
310 product line. As noted in FDA’s draft guidance for industry *Safety Considerations for Container*
311 *Labels and Carton Labeling Design to Minimize Medication Errors*, when applying color,
312 applicants “should ensure that the text highlighted by the color has adequate color contrast
313 against the background color.”⁵² In addition, “[c]olor differentiation is most effective when the
314 color used has no association with a particular feature and there is no pattern in the application of
315 the color scheme.”⁵³
316

C. Labeling Format

317
318
319 FDA requests that labeling be submitted in Microsoft Word, structured product labeling, and
320 text-based portable document format (PDF) files.⁵⁴ Labeling submitted in PDF format should be
321 text based and not scanned to enable the use of search and compare functions. Applicants should
322 also ensure consistency in the content between their different formats (i.e., in their Microsoft
323 Word, structured product labeling, and text-based PDF files). If the text of the labeling differs in
324 any of the three requested formats, applicants may be asked to resubmit their labeling for review.
325

D. Parenteral Drug Products

1. Package Type

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328
329
330 Labeling indicating the package type (i.e., single-dose, multiple-dose, or single-patient-use) for
331 ANDAs of parenteral drug products must be the same as the labeling indicating the RLD’s

⁵⁰ Id.

⁵¹ Id.

⁵² FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, at 8. When final, this guidance will represent FDA’s current thinking on this topic.

⁵³ Id.

⁵⁴ FDA draft guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*. When final, this guidance will represent FDA’s current thinking on this topic.

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332 package type.⁵⁵ For example, if the RLD is appropriately labeled and packaged in a single-dose
333 vial, the ANDA should also be labeled and packaged in a single-dose vial.

334
335 Applicants have proposed package types for parenteral drug products that differ from those
336 approved for the RLD (e.g., an applicant proposed a single-dose vial when the RLD is packaged
337 in a multi-dose vial), which resulted in a deficiency.

338 339 2. *Product Strength*

340
341 A parenteral drug product's strength is critically important information that should be clearly
342 displayed and correctly expressed on the container label to avoid dosing errors, among other
343 reasons. Overdoses have occurred with small-volume parenterals because of end-user failure to
344 determine the total amount of the drug product in the container. As described in FDA's draft
345 guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to*
346 *Minimize Medication Errors*,

347
348 [i]n most cases, the user noticed the concentration (e.g., 10 [milligrams] (mg)/[milliliter]
349 (mL)) but failed to see the net quantity (e.g., 10 mL), which often appears in a different
350 location on the container label. This confusion has led to administration of the entire
351 contents of the container, when only a portion of the total volume was needed.⁵⁶

352
353 To avoid confusion, "the strength per total volume should be the primary and prominent
354 expression on the principal display panel of the label, followed in close proximity by strength per
355 milliliter enclosed by parentheses."⁵⁷ The following format is acceptable:⁵⁸

356
357 **500 mg/10 mL**
358 (50 mg/mL)

359 360 3. *Ferrules and Cap Overseals*

361
362 The ferrules and cap overseals of injectable drug products should clearly and concisely convey
363 cautionary statements that will help prevent imminent, life-threatening situations.⁵⁹ In particular,
364 FDA recommends that the text on ferrules and cap overseals either "be limited to important
365 safety messages critical for the prevention of imminent, life-threatening situations" or remain
366 blank.⁶⁰ An example of an acceptable cautionary statement is "Warning-Paralyzing Agent."

⁵⁵ Section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314.94(a)(8)(iv).

⁵⁶ FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, at 11.

⁵⁷ *Id.*

⁵⁸ *Id.*

⁵⁹ FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. See also U.S. Pharmacopeia (USP) General Chapter <7>.

⁶⁰ FDA draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, at 17.

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367 Applicants should refer to the FDA draft guidance for industry *Safety Considerations for*
368 *Container Labels and Carton Labeling Design to Minimize Medication Errors* for further
369 information.

370
371 Applicants have submitted proposed labeling for ANDAs covering drug products with integrated
372 ferrules and cap overseals that does not convey safety information critical for the prevention of
373 imminent, life-threatening situations. In other instances, applicants have proposed labeling
374 containing information on ferrules and cap overseals that is not recommended for certain drug
375 products (e.g., some ferrules and cap overseals of injectable drug products have displayed lot
376 numbers, logos, or product names). Applicants should consider the appropriateness of including
377 or excluding such information for drug products with integrated ferrules or cap overseals because
378 this inclusion or exclusion may impact the approvability of a particular application.

379
380 In addition, FDA recommends that applicants state in Module 3.2.P.7 of their ANDA submission
381 whether text appears on the ferrule and cap overseal and, if so, what the text is. Applicants
382 should also indicate the color of the ferrule and cap overseal to ensure that the color black, which
383 is to be used only with potassium chloride injectable products, is not used for other drug
384 products.

385
386

V. PRODUCT QUALITY DEFICIENCIES

388

A. Drug Substance

389

390
391 Applicants are required to submit data and information in their ANDAs about the drug
392 substance(s) in their proposed drug products.⁶¹ To satisfy this requirement, FDA regulations
393 permit applicants either to provide this information directly in their ANDA or to reference a drug
394 master file (DMF) in their ANDA.⁶² Specifically, in their ANDA, applicants may choose to
395 either (1) include all sections of Module 3.2.S.2 or (2) reference a DMF, which should contain
396 the same information that would have been provided by the applicant in Module 3.2.S.2.

397

398 The recommendations in this section apply both to applicants that include all sections of Module
399 3.2.S.2 in their ANDAs and to DMF holders that submit DMFs to FDA.

400

401 The DMF holder is required to notify each person authorized to reference the DMF of any
402 additions, changes, or deletions to any information contained in the DMF.⁶³ Changes made to a
403 DMF referenced in an ANDA that may impact the safety, efficacy, quality, or substitutability of
404 the drug product (e.g., new facilities added by the DMF holder that need to be addressed by the
405 applicant in an amendment to the ANDA) may be considered *unsolicited amendments* to the

⁶¹ 21 CFR 314.94(a)(5).

⁶² 21 CFR 314.420(b).

⁶³ 21 CFR 314.420(c).

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406 ANDA and therefore may extend existing GDUFA review goals or create new review goals.⁶⁴ It
407 is important for applicants to be aware of when amendments will be submitted to the DMF
408 because these amendments may affect the adequacy of the DMF to support approval of the
409 ANDA.

410

411 *1. Active Pharmaceutical Ingredient Starting Material*

412 In Module 3.2.S.2, DMF holders⁶⁵ should include information on the control of materials used in
413 the manufacture of the drug substance and provide a justification for the starting material
414 selection for the process. Often, the designated starting material is a late-stage intermediate, and
415 DMF holders fail to include:

- 416 • The route of synthesis to the proposed starting material to support the starting material
417 specification (i.e., the impurity control)
418
- 419 • A discussion on the fate and purge of the potential impurities arising from the starting
420 material manufacturing process
421
- 422 • The carry-over studies of reagents/solvents into the final active pharmaceutical ingredient
423 (API)
424
- 425 • A demonstration of the suitability of analytical methods used to detect impurities in the
426 starting material
427

428 Without this information, FDA cannot assess the starting material selection and its impact on
429 both the manufacturing process and the final drug substance quality.

430 FDA recommends that DMF holders provide sufficient information, in Module 3.2.S.2, on their
431 API starting material, including the information specified in the bulleted list in this section. For
432 recommendations on the justification and selection of starting materials, DMF holders should
433 review the International Council for Harmonisation of Technical Requirements for
434 Pharmaceuticals for Human Use (ICH) guidances for industry *Q11 Development and*
435 *Manufacture of Drug Substances* and *Q11 Development and Manufacture of Drug Substances*
436 *Questions and Answers*.⁶⁶

437

438 *2. API Manufacturing Process*

⁶⁴ FDA draft guidance for industry *ANDA Submissions — Amendments to Abbreviated New Drug Applications Under GDUFA*.

⁶⁵ As noted above, the recommendations in section V.A of this guidance also apply to applicants that include all sections of Module 3.2.S.2 in their application but do not reference a DMF.

⁶⁶ ICH guidances for industry can be found on the FDA Drugs guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

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439 DMF holders should fully describe, in their DMF, their API manufacturing process, but they
440 have commonly failed to include the following information as part of a complete description of
441 the API manufacturing process:

442

- 443 • A detailed synthetic scheme
- 444 • The molar ratios of starting materials/reagents
- 445 • The reaction conditions (e.g., time and temperatures)
- 446 • A flow chart of the manufacturing process
- 447 • The batch size for each step (i.e., input/output of materials)
- 448 • The batch blending or mixing operations
- 449 • The recovered solvents, reprocessing, and reworking
- 450 • Documentation of the consistent manufacture of the claimed polymorphic form

451

452 FDA recommends that DMF holders provide complete information in Module 3.2.S.2.2 on their
453 API manufacturing process, including the information in the bulleted list above. DMF holders
454 should include a flow chart for every stage, and if the API is synthetic or semisynthetic, they
455 should provide a complete synthetic scheme from the appropriately supported starting
456 materials.⁶⁷

457

458 3. Impurities

459

460 a. API characterization information

461

462 DMF holders should include characterization information for the API, including information on
463 all potential impurities. In some cases, however, DMF holders have failed to provide
464 information on the identification and purge of impurities (i.e., process impurities and
465 degradants), including those with mutagenic potential.⁶⁸

466

467 DMF holders should include a discussion of impurities in Modules 3.2.S.2 and 3.2.S.3. For
468 information on the limits for potentially genotoxic impurities, FDA recommends that DMF
469 holders refer to the ICH guidance for industry *M7 Assessment and Control of DNA Reactive*
470 *(Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* (ICH M7).
471 Applicants should carefully assess and consider all of the control options outlined in ICH M7.

472

473 b. Safety assessment of mutagenic potential for actual and potential 474 impurities

475

476 The impurity profile of a proposed generic drug should not pose a greater mutagenic risk than the
477 RLD. DMF holders should provide an assessment of the actual and potential mutagenic

⁶⁷ FDA guidance for industry *Completeness Assessments for Type II API DMFs Under GDUFA*, at 11, and ICH guidances for industry *Q11 Development and Manufacture of Drug Substances* and *Q11 Development and Manufacture of Drug Substances Questions and Answers*.

⁶⁸ See the ICH guidance for industry *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*.

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478 impurities resulting from synthesis or degradation of the drug substance and discuss the
479 corresponding control strategy as outlined in ICH M7. The bulleted list below describes (1)
480 information DMF holders have commonly failed to include about their evaluation of actual and
481 potential genotoxic impurities, and when appropriate, (2) FDA’s recommendations on
482 conducting these evaluations:
483

484 • An assessment of potential and actual impurities with a risk assessment and a follow-up
485 evaluation of mutagenicity at the time of the DMF submission. For impurities that
486 require an evaluation of the mutagenic potential, a hazard assessment should initially
487 include conducting either (1) literature and database searches on the carcinogenicity and
488 bacterial mutagenicity potential or (2) Quantitative Structure-Activity Relationship
489 ((Q)SAR) and Structure Activity Relationship studies. Failure to include a full
490 evaluation of potential mutagenic risk at the time of the DMF submission can disrupt the
491 review process and prevent the timely review of the ANDA.

492 • Appropriate spike/purge or purging factor studies performed in a manner representative
493 of the commercial process, with a corresponding validated and fit-for-purpose analytical
494 method to support Options 3-4 described in ICH M7.⁶⁹

495 • A (Q)SAR evaluation that includes both an expert-based and a statistical-based model for
496 bacterial mutagenicity prediction. (Applicants have supplied a single model or used
497 models without submitting sufficient information on their validation.) Applicants should
498 submit full study reports for *in silico* predictions.⁷⁰

499 • An appropriately conducted *in vitro* bacterial reverse mutation assay to address a positive
500 prediction by a (Q)SAR analysis. For these assays, applicants should (1) test neat
501 impurities; (2) test concentrations up to 5,000 micrograms/plate, unless limited by
502 precipitation or cytotoxicity; and (3) adequately document that an impurity is unstable or
503 difficult to synthesize and provide a scientific justification of their due diligence to
504 synthesize the impurity.⁷¹

505 4. Specifications for Isolated Intermediates

506 DMF holders should justify their specification for isolated intermediates so that FDA reviewers
507 can understand why the DMF holder set that specification. The justification should focus on

⁶⁹ As described in ICH M7: (1) under Option 3, the DMF holder controls potentially genotoxic impurities upstream at higher than the threshold of toxicological concern with spike/purge data to less than 30% of that threshold and (2) under Option 4, the DMF holder does not use a control based on high chemical reactivity, solubility, and proven process-purging capability.

⁷⁰ For additional information, see Amberg, A, L Beilke, and J Bercu, et al., 2016, Principles and Procedures for Implementation of ICH M7 Recommended (Q)SAR Analyses, *Regul Toxicol Pharmacol*, 77:13–24; Barber, C, A Amberg, and L Custer, et al., 2015, Establishing Best Practise in the Application of Expert Review of Mutagenicity Under ICH M7, *Regul Toxicol Pharmacol*, 73:367–377.

⁷¹ ICH M7; ICH guidance for industry *S2(R1) Genotoxicity Testing and Data Interpretation for Pharmaceuticals Intended for Human Use*; and *OECD Guidelines for Testing of Chemicals, Section 4: Health Effects*, available at http://www.oecd-ilibrary.org/environment/test-no-471-bacterial-reverse-mutation-test_9789264071247-en.

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508 how the impurity specifications for the intermediates were chosen, particularly if that was the
509 only point in the process where a particular impurity was controlled. If the DMF holder did not
510 isolate an intermediate, it should explain why that was a reasonable choice. FDA also
511 recommends that DMF holders review the FDA guidance for industry *Completeness Assessments*
512 *for Type II API DMFs Under GDUFA*, which makes recommendations about the information on
513 intermediates that should be included in a DMF.

514

515 5. *Tests for Certain Critical Quality Attributes*

516 Tests for Critical Quality Attributes (CQAs) should be included in the drug substance
517 specifications, but DMF holders have failed to demonstrate a clear rationale that includes CQAs
518 when establishing drug substance specifications. DMF holders should follow the ICH limits or
519 justify their proposed limits for the existing tests (i.e., the limits for impurities, including the
520 residual solvents).

521

522 FDA recommends that DMF holders set appropriate limits based on ICH guidances for
523 industry⁷² and include a complete justification and the necessary information for qualification of
524 the limits when they exceed ICH recommendations, as explained in the FDA guidance for
525 industry ANDAs: *Impurities in Drug Substances*.

526

527 **B. Drug Product**

528

529 1. *Establishing Critical Quality Attributes*

530 CQAs describe product characteristics that are chosen to demonstrate that any given drug
531 product is of sufficient quality to ensure that drug product's safety and effectiveness. Failure to
532 establish appropriate CQAs of the proposed generic drug product (including meaningful ranges
533 or limits) may lead to a determination that the ANDA cannot be approved.

534

535 FDA recommends that applicants evaluate their drug products using (1) the general and dosage
536 form-specific recommendations for the relevant characteristics and testing described in the ICH
537 guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New*
538 *Drug Substances and New Drug Products: Chemical Substances* and (2) the recommendations
539 on quality target product profiles and CQAs in the ICH guidance for industry *Q8(R2)*
540 *Pharmaceutical Development*. In their ANDAs, applicants should include information
541 developed from their use of these two ICH guidances for industry to support their selection of
542 and rationale for CQAs.

543

544 2. *Impurities: Identification, Control, and Qualification*

545

546 a. Identifying and controlling impurities

⁷² ICH guidances for industry *Q3A Impurities in New Drug Substances*, *Q3C Impurities: Residual Solvents*, *Q3D Elemental Impurities*, and ICH M7.

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547 Applicants' identification and control of impurities are important aspects in ensuring the safety
548 of the drug product. When applicants have used inadequate protocols for generating and
549 identifying impurities and have failed to provide an appropriate rationale for their acceptance
550 criteria for impurities, FDA has refused to approve their ANDAs.

551
552 To develop acceptance criteria for impurities in generic drug products, FDA recommends that
553 applicants refer to the FDA guidance for industry *ANDAs: Impurities in Drug Products*; the
554 FDA draft guidance for industry *Elemental Impurities in Drug Products*;⁷³ the ICH guidances for
555 industry *Q3B(R2) Impurities in New Drug Products*, *Q3C Impurities: Residual Solvents*, *Q3D*
556 *Elemental Impurities*; and ICH M7.

557
558 b. Safety qualification of impurities in drug substances or drug products that
559 exceed relevant qualification thresholds

560 Generic drug formulations are expected to have the same safety profile as the RLD.⁷⁴ Applicants
561 may qualify drug substance degradants or drug product impurities either by using a comparative
562 impurity analysis with the RLD⁷⁵ or by submitting a safety justification for these impurities if
563 they exceed the relevant qualification thresholds.⁷⁶ A safety justification for impurities that
564 exceeds the relevant qualification thresholds should include an assessment of both genetic
565 toxicology and general toxicity (14- to 90-day) in a single species. Below is information that
566 applicants should include in their application but have commonly failed to include:

- 567
- 568 • Applicants should provide general toxicity information to qualify their impurity.
569 Applicants have submitted (Q)SAR evaluations to predict general toxicity, but their *in*
570 *silico* predictions have not been validated for the endpoints of a general toxicity study.
571 To address this, applicants should submit either safety information such as a repeat-dose
572 general toxicology study or published literature to characterize the safety of the impurity
573 for the intended route of administration.
 - 574 • When providing a justification that an impurity is a metabolite, applicants should provide
575 qualitative and quantitative information to support this justification. Applicants have
576 submitted qualitative information that an impurity is a metabolite but failed to provide
577 quantitative data to demonstrate the relevant systemic exposure to the proposed impurity
578 level. Applicants should provide quantitative information (e.g., plasma levels of the
579 metabolite in animals and humans at the maximum daily dose or the exposure levels in
580 animals that equals or exceeds the proposed clinical exposure levels) to demonstrate that
581 the systemic exposure is at such a level to qualify the proposed level of the impurity.

⁷³ When final, this guidance will represent FDA's current thinking on this topic.

⁷⁴ 21 CFR 314.3(a).

⁷⁵ FDA guidances for industry *ANDAs: Impurities in Drug Substances* and *ANDAs: Impurities in Drug Products*.

⁷⁶ ICH guidances for industry *Q3A Impurities in New Drug Substances* and *Q3B(R2) Impurities in New Drug Products*.

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- 582 • Applicants should provide full articles of the publications that are cited in their
583 justification to facilitate a complete review of their ANDA.

584 Applicants should submit nonclinical information to Module 4 of their submission. Applicants
585 that submit a justification for the safety of their impurities should also include references and
586 hyperlinks between related topics in the quality module (Module 3) and the nonclinical safety
587 module (Module 4).

588

589 3. *Inactive Ingredients*

590

591 a. Justification by reference to the Inactive Ingredient Database

592 Unless otherwise specified in 21 CFR 314.94(a)(9)(ii), applicants must identify and characterize
593 the inactive ingredients in their proposed drug product and provide information demonstrating
594 that these inactive ingredients do not affect the safety or efficacy of that product. The quantity of
595 an inactive ingredient in a given formulation should be based on a prior determination by FDA of
596 the safety of that inactive ingredient in an FDA-approved product. However, applicants have
597 sought approval for formulations that contain amounts of inactive ingredients at levels higher
598 than the maximums listed in the Agency’s Inactive Ingredient Database (IID)⁷⁷ without
599 providing a justification for exceeding those maximum levels.

600

601 FDA recommends that applicants (1) refer to the IID to determine the previously approved level
602 of an inactive ingredient in a given drug product and not exceed that level or (2) submit
603 controlled correspondence to the Agency requesting information on whether the use of a
604 particular inactive ingredient is acceptable in an ANDA if it is higher than the maximum listed
605 in the IID.⁷⁸ Applicants should provide an adequate justification to the Agency regarding the
606 safety of that inactive ingredient if the amount exceeds the maximum level indicated in the IID
607 for the proposed route of administration (see subsection (b) immediately below).

608

609 b. Justification of the safety of inactive ingredients in generic drug products 610 that exceed the maximum level in the IID

611

612 A generic drug formulation should include inactive ingredients that have a well-defined safety
613 profile for the proposed context of use (i.e., dose, route of administration, duration of use, and
614 patient population) and maintain a similar safety profile as the RLD. Applicants, however,
615 should provide a safety justification for inactive ingredients that exceed FDA-approved levels for
616 the route of administration. Below is information that applicants should include in a safety
617 justification for inactive ingredients that exceed FDA-approved levels:

618

- 619 • Applicants should provide a justification to demonstrate that an inactive ingredient is safe
620 for the proposed context of use (i.e., dose, route of administration, duration of use, and

⁷⁷ FDA’s IID is available at <https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm>.

⁷⁸ See FDA’s draft guidance for industry *Controlled Correspondence Related to Generic Drug Development*. When final, this guidance will represent FDA’s current thinking on this topic.

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621 patient population). Applicants have submitted justifications that fail to address context-
622 specific information that is necessary to evaluate the safety of a proposed dose, route of
623 administration, or duration of use for an inactive ingredient in a specific patient
624 population. Additionally, applicants have proposed inactive ingredients without a well-
625 established safety profile, which has led to FDA’s refusal to approve the ANDA. Generic
626 drug formulations do not undergo clinical safety studies during ANDA development, so
627 inactive ingredients without an established safety profile should not be included in a
628 generic drug formulation.

629 • Applicants should provide a complete account of the composition of complex mixtures of
630 inactive ingredients (e.g., flavors and fragrances) — including the mixtures’ individual
631 components and quantities — in either the ANDA or by referencing a DMF. Applicants
632 should identify each component of a complex mixture, including its synonyms, the
633 Chemical Abstracts Service Number, and any applicable citations to the Code of Federal
634 Regulations that are relevant to its proposed use. In addition, applicants should include
635 safety information for each component, including a history of the component’s prior use
636 and safety profile (i.e., the component’s general safety and genetic toxicity).

637 • Applicants should provide a justification supporting the safety of a proposed inactive
638 ingredient grade when relying on the established safety information from a similar grade
639 of inactive ingredient.⁷⁹ The grades of an inactive ingredient may have different
640 manufacturing processes, impurity profiles, and chemical or physical characteristics.
641 Because these factors may result in different safety profiles for each grade of inactive
642 ingredient, FDA needs sufficient details to identify the proposed inactive ingredient grade
643 and to determine whether similarities or differences between grades may affect safety.

644 4. *Validating Analytical Methods*

645 Analytical methods that applicants use for the characterization or analysis of drug products
646 should be validated by the applicant to determine if these methods are suitable for such use.
647 However, applicants have failed to appropriately validate their analytical methods, which has led
648 to incorrect results and incorrect conclusions about the drug product quality because the
649 analytical methods were not specific, accurate, or precise. This failure has contributed to FDA’s
650 refusal to approve the ANDAs.

651
652 FDA recommends that applicants (1) refer to the ICH guidance for industry *Q2(R1) Validation of*
653 *Analytical Procedures: Text and Methodology* to identify the appropriate validation of the
654 analytical methods used in their drug product analysis and (2) provide method validation reports
655 in their application.

656 657 **C. In Vitro Dissolution (Biopharmaceutics)** 658

⁷⁹ FDA guidance for industry *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.

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659 1. *Development and Validation of an In-House Dissolution Testing Method When*
660 *Dissolution Testing Cannot Be Standardized*
661

662 It is critical that applicants submit a complete method development and validation report when
663 an in-house dissolution testing method is used. Below is information that should be included in
664 the dissolution method development and validation report but applicants have commonly
665 omitted:
666

- 667 • Solubility data for the drug substance over the physiologic pH range
668
- 669 • A detailed description of both the dissolution test being proposed for the evaluation of the
670 product and the developmental parameters used to select the proposed dissolution method
671
- 672 • Data (with appropriate statistics) to support the discriminating ability of the selected
673 dissolution method related to the critical material attributes and critical process
674 parameters
675
- 676 • Complete dissolution data (i.e., individual (n=12), mean, range, and percent relative
677 standard deviation at each time point and mean profiles) and detailed information for all
678 strengths of the test product and the reference product (e.g., the batch/lot number,
679 manufacturing date, manufacturing site, testing date, and batch size) in Module 2.7.1
680
- 681 • Supportive validation data for the dissolution method (e.g., method robustness and
682 method transfer) and analytical method (e.g., specificity, precision, accuracy, linearity,
683 and stability)
684

685 FDA recommends that applicants include a summary of the in vitro dissolution development in
686 Module 3.2.P.2.2.3 with a cross-reference to studies in Module 5, as appropriate. A justification
687 for the dissolution specification should be included in Module 3.2.P.5.6. FDA also recommends
688 that applicants refer to the U.S. Pharmacopeia (USP) General Chapter <1092> and certain FDA
689 guidances for industry⁸⁰ that provide general guidelines on the development and validation of
690 dissolution procedures.
691

692 2. *Dissolution Acceptance Criteria*
693

694 The specification for solid oral dosage forms normally includes a test to measure the in vitro
695 release of a drug substance from the drug product. Applicants should provide a justification for
696 the in vitro release specification (i.e., the dissolution method and acceptance criteria) that is
697 reflective of the dissolution data from the representative batch that underwent in vivo BE testing

⁸⁰ See FDA guidance for industry *Dissolution Testing of Immediate Release Solid Oral Dosage Forms* and FDA draft guidance for industry *Dissolution Testing and Specification Criteria for Immediate-Release Solid Oral Dosage Forms Containing Biopharmaceutics Classification System Class 1 and 3 Drugs*. When final, the draft guidance will represent FDA's current thinking on this topic.

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698 (bio-batch) and supported by exhibit and registration batches that were included for stability.⁸¹
699 Below is information that should be included in the selection of dissolution acceptance criteria:

700

Immediate-release solid oral dosage forms:

702

703 • A single-point acceptance criterion where $Q=80\%$ ⁸² dissolution occurs

704

705 • The setting of the dissolution acceptance criterion, which is drug product specific and
706 based on USP Level 2 testing (n=12) (understanding that Level 2 testing and Level
707 3⁸³ testing may be needed)

708

709 • Support for a wider (i.e., more permissive) dissolution specification with an approved
710 in vitro/in vivo correlation model, a physiologically based absorption and
711 pharmacokinetic model, or a clinically relevant justification

712

Modified-release solid oral dosage forms:

714

715 • Acceptance criteria time points that cover the early, middle, and late stages of the
716 release profile

717

718 • Dissolution acceptance criteria ranges that are based on (1) a mean target value $\pm 10\%$
719 at any given time point and (2) $>80\%$ for the last specification time point

720

721 • Support for a wider (i.e., more permissive) dissolution specification with an approved
722 in vitro/in vivo correlation model, a physiologically based absorption and
723 pharmacokinetic model, or a clinically relevant justification

724

725 • A two-stage testing approach for delayed-release dosage forms

726

727 Applicants should provide a justification for the in vitro release specification in Module
728 3.2.P.5.6. Applicants should also refer to certain FDA guidances for industry⁸⁴ and ICH
729 guidance for industry⁸⁵ that provide general guidelines for dissolution specification settings. In
730 addition, the applicant's dissolution specification should not only confirm adequate formulation
731 and process control but also ensure consistent in vivo performance to the bio-batch.

⁸¹ FDA guidance for industry ANDAs: *Stability Testing of Drug Substances and Products*.

⁸² USP General Chapter <711> defines the quantity, Q , as “the amount of dissolved active ingredient specified in the individual monograph, expressed as a percentage of the labeled content of the dosage unit.”

⁸³ USP General Chapter <711>.

⁸⁴ See FDA guidances for industry *Extended Release Oral Dosage Forms: Development, Evaluation, and Application of In Vitro/In Vivo Correlations* and *Dissolution Testing of Immediate Release Solid Oral Dosage Forms*.

⁸⁵ ICH guidance for industry *Q6A Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances*.

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D. Facilities

1. Identification of Manufacturing Facilities

Applicants should provide information on their manufacturing facilities both in their Form FDA 356h and in the appropriate module within the application. However, applicants have not consistently provided (1) complete manufacturing facility information in their Form FDA 356h and (2) manufacturing facility information in the correct modules within their application, both of which have made this information not readily accessible to Agency reviewers and led to FDA’s refusal to approve the ANDAs.

For “original (initial) applications . . . CMC supplements, and resubmissions to these submission types,” applicants should include “complete information on the locations of all manufacturing, packaging, and control sites for both [the] drug substance and [the] drug product” in Form FDA 356h (i.e., the facility information that is listed in Modules 3.2.S.2 and 3.2.P.3.1).⁸⁶ Form FDA 356h should include information on:⁸⁷

- All drug product (in process material and final) manufacturing and testing sites — including the stability testing, primary packaging, and labeling sites — that are proposed to be involved in the commercial manufacture of the drug product⁸⁸
- All intermediate (i.e., performing operations governed by the ICH guidance for industry *Q7 Good Manufacturing Practice Guidance for Active Pharmaceutical Ingredients*) and final drug substance manufacturing and testing sites, including the sterilization and micronization sites, that are proposed to be involved in the commercial manufacture of the drug substance
- For combination products,⁸⁹ all manufacturing sites⁹⁰ for the non-lead constituent part of the combination product, including any separate sites responsible for design activities, that are proposed to be involved in the commercial manufacture of the finished product
- All current good manufacturing practice (CGMP) storage and warehousing facilities involved in the manufacture of the drug product

⁸⁶ Instructions for Filling out Form 356h – Application to Market a New or Abbreviated New Drug or Biologic for Human Use, available at <https://www.fda.gov/AboutFDA/ReportsManualsForms/Forms/default.htm>.

⁸⁷ See 21 CFR 314.50.

⁸⁸ FDA does not recommend listing facilities (1) that have not performed any functions or (2) for which a technology transfer of data has not occurred.

⁸⁹ See 21 CFR 3.2(e).

⁹⁰ See 21 CFR 4.

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767 Applicants do not need to list “bioequivalence testing sites, excipient testing sites, and
768 container/closure manufacturing and testing establishments” on their Form FDA 356h.⁹¹

769
770 Module 3.2.S.2 should include all manufacturing facilities that are listed on Form FDA 356h as
771 well as all research and development manufacturing and testing sites that generated data to
772 support the application in accordance with 21 CFR 314.50(d)(1)(ii)(b). Applicants should list all
773 laboratories that perform testing, including drug substance characterization and method
774 comparisons, and functions integral to the control strategy. This module should also include any
775 testing sites that generate stability testing or release data to support the application as well as the
776 testing sites for the planned commercial testing.

777 778 2. *Readiness for Inspection*

779
780 All manufacturing facilities should be ready for inspection at the time of the ANDA submission,
781 and applicants should indicate whether each site is ready for inspection on their Form FDA 356h.
782 In the past, applicants have specified on Form FDA 356h that a manufacturing facility was ready
783 for inspection, but once FDA was ready to commence inspection, the manufacturing facility
784 indicated it was not ready for this inspection, which has led to FDA’s refusal to approve the
785 ANDAs.

786
787 If there are extenuating circumstances that prevent a facility from being ready for inspection,
788 applicants should indicate this on Form FDA 356h. FDA considers it a good business practice
789 for applicants to regularly communicate with manufacturing facilities, including contract
790 manufacturing facilities, about changes in their inspection status to prevent any problems that
791 may delay approval of their application.

792 793 3. *Selection of Contract Manufacturing Facilities and CGMPs*

794
795 Applicants should consider several factors in selecting suitable contract manufacturing facilities,
796 including their manufacturing capability for the product and compliance with CGMPs. In the
797 application, applicants should certify that contract manufacturing facilities are compliant with
798 CGMPs.⁹² FDA has observed that applicants have certified that contract manufacturing facilities
799 are CGMP compliant, but upon assessment or inspection, FDA determined that they were not
800 compliant at the time of the ANDA submission, which caused the ANDA to not be approved.

801
802 FDA recommends that applicants and contract manufacturing facilities clearly define the CGMP-
803 related roles and manufacturing operations and activities of each of the parties in a quality
804 agreement.⁹³ A quality agreement should clearly describe the materials or services to be

⁹¹ Instructions for Filling out Form 356h – Application to Market a New or Abbreviated New Drug or Biologic for Human Use.

⁹² Section 505(j)(4) of the FD&C Act states that FDA shall approve an ANDA unless “the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity.” See also FDA’s draft guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*.

⁹³ FDA guidance for industry *Contract Manufacturing Arrangements for Drugs: Quality Agreements*.

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805 provided, quality specifications, and communication mechanisms between the applicant and the
806 contract manufacturing facility.

807

E. Commercial Manufacturing Process

809

810 Applicants should provide — in Modules 3.2.P.2, 3.2.P.3, and 3.2.R — both details of the
811 commercial manufacturing process and information to support the use of that particular process.
812 These details and information help FDA determine whether applicants are ready to commercially
813 manufacture a drug product. However, applicants often provide inconsistent, inaccurate, or
814 incomplete information in these modules, leading to refusals to approve. Below is information
815 that should be included in these modules:

816

817 • Applicants should provide, in Module 3.2.P.2, a justification for their process selection
818 that relies on established scientific principles to identify potential risks to their
819 manufacturing process. This justification should include batch data (from the exhibit
820 and/or development batches) that demonstrate that any risks to the manufacturing process
821 are adequately mitigated. Applicants should also include a discussion of their risk
822 mitigation approaches and explain any differences between the exhibit and commercial
823 batches regarding their manufacturing processes and in-process controls.

824

825 • Applicants should demonstrate that their proposed control strategy will ensure that the
826 quality of the intermediate critical material attributes will remain unchanged across the
827 exhibit and commercial batches. Applicants should clearly identify and justify, in
828 Module 3.2.P.3.4, the in-process controls utilized in the exhibit and commercial batch
829 manufacturing processes.

830

831 • The commercial batch formula identified in Module 3.2.P.3.2 should (1) reflect the unit
832 dose composition identified in Module 3.2.P.1 and (2) clearly identify and justify any
833 overage and overfill used. Applicants should provide a table comparing the quantity and
834 the quality standard of each ingredient, including any solvents removed during the
835 process, used in the exhibit and commercial batches.⁹⁴

836

837 • Applicants should demonstrate a readiness for the commercial scale manufacture of the
838 drug product by providing the set points and ranges of the commercial scale process
839 parameters in the commercial equipment. Applicants should also clearly identify and
840 justify, in Module 3.2.P.3, any differences in the equipment used for the exhibit and
841 commercial batches, as well as provide process parameters that are (1) scaled-up using
842 established principles, (2) supported by process development data, and (3) specified (i.e.,
843 “To Be Determined” should not be used) and not open-ended (e.g., no more than 200
844 revolutions per minute).

845

⁹⁴ Please note that FDA may request the manufacture of a new batch if there are inappropriate overages, overfills, or composition differences in the exhibit and commercial batches.

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- Applicants should use a table, in Module 3.2.P.3.3, to submit the hold times and hold conditions of the intermediates and bulk drug products used in the commercial process.
 - Executed batch records provided in Module 3.2.R should clearly specify the batch usage (e.g., development and stability) for each submitted executed batch record. In particular, the batch used for BE testing should be noted along with the BE study identifier.

F. Microbiology Considerations

1. In-Process Bioburden Testing and Acceptance Criteria

856

857 An ANDA for an aseptically processed generic drug product should contain in-process

858 acceptance criteria for the total number of microorganisms associated with the unfiltered bulk

859 drug solution prior to its sterilization (bioburden) because the “bioburden can contribute

860 impurities (e.g., endotoxin) to, and lead to degradation of, the drug product.”⁹⁵ Applicants have

861 commonly submitted ANDAs for drug products without providing bioburden testing and in-

862 process bioburden acceptance criteria for the bulk drug solution prior to any filtration, which has

863 led to FDA’s refusal to approve the ANDAs.

864

865 As described in the guidances for industry *For the Submission of Documentation for Sterilization*

866 *Process Validation in Applications for Human and Veterinary Drug Products* and *Sterile Drug*

867 *Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, FDA

868 recommends that applicants both establish a prefiltration bioburden acceptance criteria and

869 design manufacturing process controls to minimize the bioburden in the bulk drug solution prior

870 to sterilization.

2. Description and Validation of Bacterial Endotoxins Test Method

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872

873

874 An application for a parenteral generic drug product with a product endotoxin specification

875 should contain both a description and validation of the bacterial endotoxins test method used.

876 However, applicants have submitted ANDAs for parenteral generic drug products with a product

877 endotoxin specification that have not described the bacterial endotoxins test method used,

878 including the sample preparation and routine test dilution. Without this test method description,

879 the Agency has been unable to determine whether the bacterial endotoxins method was

880 adequately validated, which has led to FDA’s refusal to approve the ANDAs. For the bacterial

881 endotoxins method validation, applicants have not always accounted for the additional dilution

882 that resulted from sample pooling in maximum valid dilution (MVD) calculations, which has

883 again led to FDA’s refusal to approve the ANDAs.

884

⁹⁵ FDA guidance for industry *Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice*, at 36.

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885 Applications for parenteral generic drug products with a product endotoxin specification should
886 contain a description and validation of the endotoxins test method used,⁹⁶ including any test
887 sample pooling and dilution performed routinely for method validation. In validating the chosen
888 test method, applicants should understand that FDA generally accepts sample pooling for

889
890 small-volume parenterals (those with volumes of 100 mL or less) as long as the
891 MVD is adjusted to a proportional, lower value because of the potential for
892 diluting a unit containing harmful levels of endotoxins with other units containing
893 lower, less harmful, levels of endotoxins. This “adjusted MVD” is obtained by
894 dividing the MVD computed for an individual sample by the total number of
895 samples to be pooled If this reduction in MVD results in an inability to
896 overcome product-related assay interference because of an insufficient dilution,
897 then the samples should be tested individually.⁹⁷

898 3. Microbiological Data To Support Extended Storage Times

900
901 If the proposed generic drug product is sterile, then the extended post-constitution and/or post-
902 dilution storage times in the draft labeling should be supported by microbiological data. This
903 data should demonstrate that the drug product does not support microbial growth from
904 inadvertent contamination over the storage periods/conditions described in the labeling.

905
906 FDA recommends that applications contain a summary of the microbiological study, including
907 the challenge organisms and challenge titers, the product sample concentrations and storage
908 conditions, the diluents tested, and a summary of the study results. In addition, applicants should
909 refer to FDA’s *Question-based Review (QbR) for Sterility Assurance of Terminally Sterilized*
910 *Products: Quality Overall Summary Outline*,⁹⁸ *Question-based Review (QbR) for Sterility*
911 *Assurance of Terminally Sterilized Products: Frequently Asked Questions*,⁹⁹ and *Question-*
912 *based Review (QbR) for Sterility Assurance of Aseptically Processed Products: Quality Overall*
913 *Summary Outline*.¹⁰⁰

914
915

⁹⁶ FDA guidances for industry *Pyrogen and Endotoxins Testing: Questions and Answers*, at 4, and *For the Submission of Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*, at 8.

⁹⁷ FDA guidance for industry *Pyrogen and Endotoxins Testing: Questions and Answers*, at 4.

⁹⁸ This document is available at <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM276168.pdf>.

⁹⁹ This document is available at <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM276170.pdf>.

¹⁰⁰ This document is available at <https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM401339.pdf>.

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916 VI. BIOEQUIVALENCE DEFICIENCIES

917

918 A. Bioanalytical Study Data

919

920 It is critical for applicants to submit complete bioanalytical study reports and to validate
921 bioanalytical methods used in their BE studies. Below is information that should be included in
922 an application's bioanalytical study report:

923

- 924 • Complete dilution integrity data, stock stability data, and recovery data
- 925 • Analytical raw data from the study runs (accepted and rejected) of all subjects
- 926 • Serially selected chromatograms for 20% of the study subjects
- 927 • Bioanalytical standard operating procedures used in the application

928

929 FDA recommends that applicants submit complete bioanalytical reports and review the FDA
930 draft guidance for industry *Bioanalytical Method Validation*¹⁰¹ to help ensure that applicants
931 provide the bioanalytical method validation data needed for FDA's review of the ANDA.
932 Providing complete bioanalytical study reports and bioanalytical methodology validation data
933 will help ensure that FDA has the information required to determine whether the method used
934 was suitable and reliable.

935

936 B. Clinical Summary

937

938 Applicants should submit clinical summary data from in vivo BE studies that are critical to
939 FDA's determination of BE. To help applicants summarize this data,

940

941 FDA has developed model summary tables The[se] tables provide a format
942 for applicants to summarize various aspects of the BE submission such as the
943 design and outcome of in vivo and in vitro BE studies as well as the results of in
944 vitro dissolution testing.¹⁰²

945

946 Applicants can find these model tables on the FDA ANDA Forms and Submission Requirements
947 website.¹⁰³

948

949 Applicants, however, have submitted summary tables that are neither filled out completely nor
950 prepared properly. For example, applicants have failed to list, in formulation tables, all of the
951 strengths of the products for which they are seeking approval. Applicants have also submitted

¹⁰¹ When final, this guidance will represent FDA's current thinking on this topic.

¹⁰² FDA draft guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*, at 10-11.

¹⁰³ These tables are available at <https://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120955.htm>. Applicants should periodically refer to that website because the Agency may update the existing tables or add new tables to address both additional study types and waiver requests.

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952 summary tables to FDA in a scanned document rather than in a text-based PDF file and
953 Microsoft Word document. These actions have led to FDA’s refusal to approve the ANDAs.

954
955 FDA recommends that applicants provide accurate and complete information in their model
956 summary tables. Applicants should submit summary tables for all studies conducted, whether
957 they were passing or failing studies,¹⁰⁴ in a text-based PDF file and Microsoft Word
958 document.¹⁰⁵

C. Deviations from Product-Specific Guidances

960
961 Applicants that deviate from a relevant product-specific guidance¹⁰⁶ should provide a detailed
962 justification for this deviation, as well as data to support this deviation, in their original ANDA
963 submission. Below is information that should be included, as applicable:

- 964
965 • A detailed justification for and data (such as their inclusion/exclusion criteria or
966 demographic information) to support why their use of a particular study population does
967 not affect their BE determination
- 968
969 • A detailed explanation of how any deviation in their primary endpoint from the product-
970 specific guidance is as sensitive as the product-specific guidance’s endpoint for detecting
971 differences between the RLD and the generic product
- 972
973 • A detailed justification, in their protocol and Statistical Analysis Plan, for why their
974 proposed prespecified statistical method is different from the product-specific guidance’s
975 recommendation
976

D. Information on BE and Safety Related to In Vivo BE Studies

977
978 In original ANDA submissions, applicants should include all of the BE and safety information
979 related to the conduct of in vivo BE studies that is listed in the FDA draft guidance for industry
980 *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*. However,
981 applicants have not always included in their original ANDAs the information that is necessary
982 for FDA to fully evaluate the BE of the test product in a timely manner, resulting in FDA’s
983 refusal to approve the ANDAs. Below is information that applicants should provide:

- 984
985 • To ensure the welfare of human subjects involved in comparative clinical BE studies,
986 applicants should provide, with dates, their protocol, Institutional Review Board approval
987 forms, and consent forms. If their protocol was amended after the study was initiated,
988 applicants should highlight the changes, compare the original protocol with the amended
989

¹⁰⁴ FDA guidance for industry *Submission of Summary Bioequivalence Data for ANDAs*.

¹⁰⁵ FDA draft guidance for industry *ANDA Submissions — Content and Format of Abbreviated New Drug Applications*, at 11.

¹⁰⁶ FDA regularly publishes product-specific guidances that describe the Agency’s current thinking and expectations on how to develop generic drug products that are therapeutically equivalent to the RLD.

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990 protocol, and provide an explanation for why the change did not affect the safety or
991 efficacy of the study product.

- 992
- 993 • For subjects with serious adverse events, who died, or became pregnant, applicants
994 should provide a written narrative that provides complete follow-up details on the
995 condition of the subjects so that the Agency can complete a comprehensive review of
996 safety reports for the generic drug product. In particular, if a pregnancy follow-up is not
997 complete at the time of the original ANDA submission, applicants should provide
998 updates (such as whether the pregnancy resulted in a live birth) as soon as the
999 information becomes available.

1000 **E. Differences in Formulations and Inactive Ingredients**

1001

1002 For drug products for parenteral use, applicants should provide a clear justification and
1003 documentation for any differences permissible under FDA regulations between the formulation
1004 of the proposed generic drug product and the formulation of the RLD.¹⁰⁷ In addition, if
1005 applicants used inactive ingredients or amounts of inactive ingredients in their placebo test
1006 formulation used for BE testing that were different than the inactive ingredients or amounts of
1007 inactive ingredients in the proposed generic drug product formulation, they should provide a
1008 rationale and documentation in their original ANDA submission that explains why these
1009 differences did not affect their demonstration of BE of the proposed generic drug product to the
1010 RLD. Applicants, however, have commonly failed to provide necessary justifications and
1011 documentation for these differences, which has led to FDA's refusal to approve the ANDAs.

1012 **F. Waiver Requests Under 21 CFR 314.99(b)**

1013

1014

1015 Applicants have submitted ANDAs for formulations for products for ophthalmic or otic use that
1016 are not qualitatively and quantitatively (Q1/Q2) the same as the approved RLD's formulation but
1017 for which Q1/Q2 sameness is required under FDA's regulations.¹⁰⁸ When an applicant has
1018 sought approval for a formulation that is Q1/Q2 the same as the formulation previously marketed
1019 by the innovator, FDA has determined that, in appropriate circumstances, under 21 CFR
1020 314.99(b), it may waive the requirement in the regulation that the inactive ingredients approved
1021 in the drug product under an ANDA be the same as those in the current formulation of the RLD
1022 if the statutory requirement regarding safety of inactive ingredients has been met.

1023

1024 FDA recommends that ANDA applicants:

1025

¹⁰⁷ See, e.g., 21 CFR 314.94(a)(9)(iii).

¹⁰⁸ 21 CFR 314.94(a)(9)(iii) and 21 CFR 314.94(a)(9)(iv). Generally, a generic drug product is considered qualitatively and quantitatively the same as the RLD if the concentration or amount of each inactive ingredient in the test product differs by no more than +/- 5% of the concentration or amount for the same ingredient in the RLD.

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- Determine whether they are seeking approval of a drug product where Q1/Q2 sameness to the RLD is required but the proposed generic product duplicates a previously approved (and not current) formulation of the RLD¹⁰⁹
 - Consider submitting a request for waiver of the above-identified regulatory requirements under 21 CFR 314.99(b)
- FDA will determine whether to grant a waiver under 21 CFR 314.99(b) during its substantive review of the ANDA.

¹⁰⁹ 21 CFR 314.127(a)(8).