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# Referencing Approved Drug Products in ANDA Submissions

## 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### *DRAFT GUIDANCE*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)**

**January 2017  
Generics**

# Referencing Approved Drug Products in ANDA Submissions

## Guidance for Industry

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

*Draft — Not for Implementation*

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1 **Referencing Approved Drug Products in ANDA Submissions**  
2 **Guidance for Industry<sup>1</sup>**  
3

4  
5 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
6 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
7 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
8 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
9 for this guidance as listed on the title page.  
10

11  
12  
13 **I. INTRODUCTION**  
14

15 This guidance is intended to provide information to potential applicants on how to identify a  
16 reference listed drug (RLD), reference standard, and the basis of submission in an abbreviated  
17 new drug application (ANDA) submission.<sup>2</sup>  
18

19 Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) permits any person to  
20 submit to the Food and Drug Administration (FDA or the Agency) an ANDA to seek approval to  
21 market a generic drug.<sup>3</sup> FDA’s regulations use certain terms for products that relate to an  
22 ANDA. In general, to obtain approval of an ANDA for a generic drug, an ANDA applicant first  
23 must identify the previously approved drug product it seeks to duplicate, i.e., the *reference listed*  
24 *drug (RLD)*, and must show, among other things, that the generic drug is bioequivalent to the  
25 RLD. A *reference standard* selected by FDA is the specific drug product that the ANDA  
26 applicant must use in conducting any in vivo bioequivalence testing required to support approval  
27 of its ANDA. The reference standard, selected by FDA, is ordinarily the RLD. However, there  
28 may be circumstances (e.g., where the RLD is no longer marketed) in which the reference  
29 standard is a drug product other than the RLD. FDA regulations require an ANDA applicant to  
30 include in an ANDA its “basis for ANDA submission” (referred hereinafter as “basis of  
31 submission”).<sup>4</sup> The basis of submission includes, among other things, the name of the RLD.  
32

33 A variety of factors has led to confusion among stakeholders on what the terms RLD, reference  
34 standard, and basis of submission mean, and how ANDA applicants should use them. These  
35 factors include the discontinued marketing of many approved drug products and FDA’s  
36 identification of reference standards with the RLD symbol (“+”) in the printed version, and under

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<sup>1</sup> This guidance has been prepared by the Office of Generic Drugs in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration.

<sup>2</sup> An ANDA includes all amendments and supplements to the application. 21 CFR 314.3(b). FDA recently revised certain regulations in parts 314 and 320 and this guidance refers to the regulations as revised. See *Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule*, 81 FR 69580 (October 6, 2016).

<sup>3</sup> Throughout this guidance we use the term *generic drug* to refer to a new drug product described in an ANDA submitted under section 505(j) of the FD&C Act.

<sup>4</sup> 21 CFR 314.94(a)(3).

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37 the “RLD” column in the electronic version, of FDA’s *Approved Drug Products with*  
38 *Therapeutic Equivalence Evaluations* (the Orange Book).

39  
40 The purpose of this guidance is to address this confusion by explaining what these terms mean  
41 and clarifying the differences among them. This guidance provides recommendations on how  
42 applicants can accurately use these terms in an ANDA, how persons can request FDA  
43 designation of an RLD, and how persons can request FDA selection of a reference standard.  
44 Because of the confusion regarding use of these terms up until now, previously issued CDER  
45 guidances may not use these terms as we are clarifying them in this guidance.

46  
47 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
48 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
49 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
50 the word *should* in Agency guidances means that something is suggested or recommended, but  
51 not required.

52

### **II. BACKGROUND**

53

54  
55 The process for obtaining approval to market an innovator drug approved under a new drug  
56 application (NDA) differs from that for obtaining approval to market a generic drug under an  
57 ANDA. An NDA for an innovator drug must contain, among other things, a demonstration of  
58 the safety and effectiveness of the drug for the conditions of use for which approval is sought.<sup>5</sup>  
59 A 505(b)(1) application, also known as a “stand-alone” NDA, is an application that contains full  
60 reports of investigations of safety and effectiveness that were conducted by or for the applicant  
61 or for which the applicant has a right of reference or use. A 505(b)(2) application is an NDA that  
62 contains full reports of investigations of safety and effectiveness, where at least some of the  
63 information required for approval comes from studies not conducted by or for the applicant and  
64 for which the applicant has not obtained a right of reference or use (e.g., published literature).  
65 Both 505(b)(1) and 505(b)(2) applications are approved under section 505(c) of the FD&C Act.

66

67 To obtain approval for a generic drug, an ANDA applicant is not required to provide independent  
68 evidence of the safety and effectiveness of the proposed generic drug. Instead, the applicant  
69 relies on FDA’s finding that a previously approved drug product, i.e., the RLD, is safe and  
70 effective, and must demonstrate, among other things, that the proposed generic drug is the *same*  
71 as the RLD in certain ways. Specifically, with limited exceptions described in this section, a  
72 drug product for which an ANDA is submitted must have, among other things, the same active  
73 ingredient(s), conditions of use, route of administration, dosage form, strength, and (with certain  
74 permissible differences) labeling as the RLD.<sup>6</sup> An ANDA applicant also must demonstrate that  
75 its proposed generic drug is bioequivalent to the RLD,<sup>7</sup> and if in vivo bioequivalence studies are  
76 required for approval of the ANDA, the applicant must use the reference standard selected by

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<sup>5</sup> Section 505(b)(1) of the FD&C Act.

<sup>6</sup> Section 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act; see also 21 CFR 314.94(a).

<sup>7</sup> Section 505(j)(2)(A)(iv) of the FD&C Act

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77 FDA in such testing. A generic drug must meet the same high standards of quality and  
78 manufacturing as drug products approved under section 505(c) of the FD&C Act.<sup>8</sup>

79  
80 FDA’s approval of an ANDA reflects the Agency’s determination that the proposed generic drug  
81 is therapeutically equivalent to its RLD. Therapeutic equivalents are approved drug products  
82 that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that  
83 can be expected to have the same clinical effect and safety profile when administered to patients  
84 under the conditions specified in the labeling.<sup>9</sup>

85  
86 To submit an ANDA for a generic drug that is not the *same* as its RLD because it has one  
87 different active ingredient (in a fixed combination drug product), or has a different route of  
88 administration, dosage form, or strength than that of the RLD, an applicant first must obtain  
89 permission from FDA through the citizen petition process.<sup>10</sup> Such petitions are referred to as  
90 *suitability petitions*. FDA would not approve a suitability petition if, for instance, investigations  
91 must be conducted to show the safety and effectiveness of the proposed generic drug.<sup>11</sup>

### 92 93 **III. DISCUSSION**

#### 94 95 **A. Listed Drug**

96  
97 FDA regulations define a “listed drug” as “a new drug product that has been approved under  
98 section 505(c) of the [FD&C Act] for safety and effectiveness or under section 505(j) of the  
99 [FD&C Act], which has not been withdrawn or suspended under section 505(e)(1) through (5) or  
100 section (j)(6) of the [FD&C Act], and which has not been withdrawn from sale for what FDA has  
101 determined are reasons of safety or effectiveness.”<sup>12</sup> Drug products approved under an NDA,  
102 either through a 505(b)(1) application or a 505(b)(2) application, may be listed drugs. Likewise,  
103 a drug product approved under an ANDA may be a listed drug. A drug product is deemed to be  
104 a listed drug on the date of approval of the NDA or ANDA for the drug product.<sup>13</sup> Each strength  
105 of a drug is a distinct drug product and, therefore, a distinct listed drug. Listed drugs appear in  
106 FDA’s Orange Book.<sup>14</sup>

107  
108 When a drug product is approved, generally it appears in the Orange Book section entitled the  
109 “Prescription Drug Product List” or the “Over-the-Counter Drug Product List;” these sections are  
110 commonly referred to as the *Active Sections*. When an approved drug product is not marketed,

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<sup>8</sup> Section 505(j)(2)(A)(vi) of the FD&C Act.

<sup>9</sup> See 21 CFR 314.3(b). Pharmaceutical equivalents are drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. See 21 CFR 314.3(b).

<sup>10</sup> Section 505(j)(2)(C) of the FD&C Act; 21 CFR 314.93(b).

<sup>11</sup> 21 CFR 314.93(e)(1)(i).

<sup>12</sup> 21 CFR 314.3(b); see also section 505(j)(7) of the FD&C Act.

<sup>13</sup> 21 CFR 314.3(b).

<sup>14</sup> The Orange Book is available at <http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm>.

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111 FDA moves the drug product to the Orange Book’s “Discontinued Drug Product List,” which is  
112 commonly referred to as the *Discontinued Section*. In general, a listed drug is moved to the  
113 Discontinued Section when the applicant notifies FDA that it is withdrawing the listed drug from  
114 sale<sup>15</sup> or FDA otherwise determines that the listed drug has been withdrawn from sale. A listed  
115 drug also may be moved to the Discontinued Section if the applicant requests that approval of the  
116 NDA or ANDA be withdrawn because the drug product is no longer being marketed.<sup>16</sup>

### **B. Reference Listed Drug**

#### *1. FDA’s Identification of listed drugs that have been designated as RLDs*

122 The FD&C Act and FDA’s regulations require an ANDA applicant to “refer” in its ANDA to the  
123 specific listed drug on which the applicant relies in seeking approval of its ANDA.<sup>17</sup> This listed  
124 drug is the RLD.<sup>18</sup>

126 Because an ANDA applicant is relying on FDA’s finding that the RLD is safe and effective, the  
127 RLD is a drug product approved under section 505(c) of the FD&C Act for which FDA has  
128 made a finding of safety and effectiveness.<sup>19</sup> FDA identifies in the Orange Book listed drugs  
129 that are eligible to be RLDs. Generally, FDA will not designate a drug product approved  
130 through the 505(b)(2) pathway as an RLD if a drug product with the same active ingredient,  
131 dosage form, route of administration, and strength has been approved in a 505(b)(1) application.  
132 However, to ensure that a drug product approved in a 505(b)(2) application is not shielded from  
133 generic competition (e.g., where the drug product approved in a 505(b)(2) application has a  
134 different indication than the drug product approved in a 505(b)(1) application), FDA may  
135 designate the drug product approved in a 505(b)(2) application as an additional RLD if requested  
136 to do so.

138 A listed drug approved under section 505(c) that appears in an Active Section of the Orange  
139 Book may be eligible to be an RLD. A listed drug approved under section 505(c) that appears in  
140 the Discontinued Section also may be eligible to be an RLD, unless FDA makes a determination  
141 that the listed drug was withdrawn from sale for reasons of safety or effectiveness. If FDA  
142 makes such a determination, the listed drug will be removed from the Orange Book and is no

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<sup>15</sup> An applicant must report its withdrawal of a listed drug from sale within 15 working days of the withdrawal. 21 CFR 314.81(b)(3)(iv).

<sup>16</sup> An applicant may request that approval of an NDA or ANDA be withdrawn because the drug product that is the subject of the NDA or ANDA is no longer being marketed. 21 CFR 314.150(c). FDA will withdraw approval of the NDA or ANDA based on the applicant’s request provided none of the conditions in 314.150(a) or (b) applies.

<sup>17</sup> Section 505(j)(2) of the FD&C Act; 21 CFR 314.94(a)(3).

<sup>18</sup> 21 CFR 314.3(b). There may be multiple approved drugs each of which may be eligible to be an RLD for a particular drug product, e.g., either Trandate 100 mg tablets (NDA 018716) or Normodyne 100 mg tablets (NDA 018687) are eligible to be the RLD for an ANDA for Labetalol Hydrochloride 100 mg tablets.

<sup>19</sup> The principles in this draft guidance focus on the appropriate identification of products referred to in ANDAs for generic drugs that are intended to duplicate listed drugs approved after enactment of the *Drug Price Competition and Patent Term Restoration Act of 1984* (Pub.L. 98-417), commonly referred to as the Hatch-Waxman Amendments. If an applicant is seeking approval of an ANDA that is intended to duplicate a listed drug approved prior to enactment of the Hatch-Waxman Amendments, the applicant may consult the Agency if it has questions regarding appropriate identification of products.

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143 longer eligible to be an RLD. Under FDA regulations, the Agency may determine at any time  
144 whether a listed drug was withdrawn from sale for reasons of safety or effectiveness. However,  
145 FDA must determine whether a listed drug was withdrawn from sale for reasons of safety or  
146 effectiveness before FDA: (1) can approve an ANDA that refers to the listed drug as its RLD; (2)  
147 whenever the listed drug is voluntarily withdrawn from sale if any approved ANDA already  
148 refers to that listed drug; and (3) when any person petitions for such a determination.<sup>20</sup> These  
149 determinations are completed by the Agency and subsequently are published in the Federal  
150 Register.<sup>21</sup> Historically FDA generally did not approve ANDAs for which the Agency had made  
151 a determination that the RLD was not withdrawn from sale for reasons of safety or effectiveness  
152 until after that determination was published in the Federal Register. In order to expedite the  
153 availability of generic drugs, FDA now will approve a generic drug for which it has made a final  
154 determination that the RLD was not withdrawn from sale for safety or effectiveness reasons even  
155 if that determination has not yet published in the Federal Register, and will proceed with Federal  
156 Register publication as expeditiously as is practicable.

157  
158 If FDA determines that a listed drug in the Discontinued Section was not withdrawn from sale  
159 for safety or effectiveness reasons and publishes that determination in the Federal Register, the  
160 Agency generally adds the following notation to that product listing information in the Orange  
161 Book: “\*\*Federal Register determination that product was not discontinued or withdrawn for  
162 safety or efficacy reasons\*\*”.<sup>22</sup> If FDA determines that the listed drug was withdrawn from sale  
163 for reasons of safety or effectiveness, the Agency will remove the listed drug from the Orange  
164 Book and the Agency will not accept for review or approve ANDAs that refer to the drug  
165 product.<sup>23</sup>

### 2. *Choosing an RLD*

166  
167  
168  
169 An ANDA applicant must first choose an RLD. If FDA has not designated an RLD for a drug  
170 product the applicant intends to duplicate, the potential applicant may submit controlled  
171 correspondence to FDA asking FDA to designate an RLD for that drug product.<sup>24</sup> If FDA has  
172 designated a listed drug as an RLD, but the potential applicant intends to refer to a different  
173 listed drug that is a pharmaceutical equivalent to the drug designated as an RLD, the potential  
174 applicant may submit a citizen petition under 21 CFR 10.25(a) and 10.30 to request that FDA  
175 designate that different listed drug as an additional RLD. If an RLD appears in the Discontinued  
176 Section and FDA has not yet made a determination whether the drug was withdrawn from sale  
177 for reasons of safety or effectiveness, the applicant must submit a citizen petition under 21 CFR

---

<sup>20</sup> 21 CFR 314.161(a).

<sup>21</sup> See, e.g., Determination that KENALOG (Triamcinolone Acetonide) Lotion and Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness (81 FR 13797; March 15, 2016); and Determination that Ondansetron (Ondansetron Hydrochloride) Injection, USP, in PL 2408 Plastic Container, 32 Milligrams in 50 Milliliters, Was Withdrawn From Sale for Reasons of Safety or Effectiveness (80 FR 32962; June 10, 2015).

<sup>22</sup> The Orange Book may not include notations for all such determinations and does not reflect determinations made before 1995. A potential applicant should refer to the Federal Register to see if FDA has made a determination about whether a listed drug has been voluntarily withdrawn from sale for safety or effectiveness reasons.

<sup>23</sup> 21 CFR 314.162(a).

<sup>24</sup> See FDA’s guidance for industry on *Controlled Correspondence Related to Generic Drug Development* (Sept. 2015).



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178 10.25(a) and 10.30, at the same time as the ANDA submission, seeking a determination whether  
179 the listed drug has been withdrawn from sale for safety or effectiveness reasons.<sup>25</sup> Such petition  
180 must contain all evidence available to the petitioner concerning the reason that the drug product  
181 was withdrawn from sale.<sup>26</sup>

182  
183 If an applicant has a question about which listed drug it should identify as the RLD, the applicant  
184 may consult the Agency.

### 185 186 3. *The Role of an RLD in an ANDA*

187  
188 The RLD is the listed drug to which the ANDA applicant must show its proposed generic drug is  
189 the same with respect to active ingredient(s), dosage form, route of administration, strength,  
190 labeling, and conditions of use, among other characteristics.

191  
192 Regarding the *same labeling* requirement, the generic drug must have the same labeling as the  
193 RLD, except for differences permitted under the FD&C Act and Agency regulations.<sup>27</sup>  
194 Accordingly, an ANDA applicant must compare its proposed product's labeling to that of the  
195 RLD, even if FDA has selected a new *reference standard* for use in in vivo bioequivalence  
196 studies, as described in detail in section III.C. below.<sup>28</sup> Similarly, in evaluating drug product  
197 formulation and inactive ingredients, an ANDA applicant must compare its proposed generic  
198 drug to the RLD's formulation, not the formulation of the reference standard.

199  
200 For an ANDA based on an approved suitability petition (a *petitioned ANDA*), the RLD is the  
201 listed drug referenced in the approved suitability petition.<sup>29</sup>

202  
203 Prior to 2017, the column in the electronic Orange Book labeled "RLD", and the symbol in the  
204 printed version described as identifying the RLD, at times indicated the drug product FDA  
205 selected as the reference standard and at other times indicated the RLD, contributing to the  
206 confusion about which drug is the RLD and which drug is the reference standard. Starting in  
207 2017, FDA intends to modify the Orange Book to clarify which listed drugs are RLDs and which  
208 are reference standards, and to indicate which products in the Discontinued Section may be

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<sup>25</sup> 21 CFR 314.122(a). If the listed drug is moved to the Discontinued Section while the ANDA is pending, a safety and effectiveness determination must be made by FDA before the ANDA can be approved. 21 CFR 314.161(a)(1).

<sup>26</sup> 21 CFR 314.122(a).

<sup>27</sup> The FD&C Act and FDA's regulations permit labeling differences because of differences approved under a suitability petition or because the generic drug and the RLD are produced or distributed by different manufacturers. Section 505(j)(4)(G) of the FD&C Act and 21 CFR 314.94(a)(8)(iv). In certain instances, the labeling for the generic drug may differ from the labeling for the RLD if FDA permits the ANDA applicant to omit (*carve out*) protected conditions of use from labeling and obtain approval for conditions of use that are not covered by unexpired patents or exclusivity. See, e.g., Section 505(j)(2)(A)(viii) of the FD&C Act; 21 CFR 314.127(a)(7).

<sup>28</sup> An applicant is responsible for checking appropriate sources in order to obtain the RLD labeling. In instances where the RLD labeling cannot be located, an applicant for convenience initially may compare its proposed generic drug's labeling with the labeling of another ANDA that referenced the same RLD and currently is marketed. Prior to approval, the applicant may need to revise labeling to reflect certain updated information that would have been necessary had the RLD not been withdrawn. See FDA's draft guidance for industry on *Updating ANDA Labeling After the Marketing Application for the Reference Listed Drug Has Been Withdrawn* (July 2016).

<sup>29</sup> 21 CFR 314.94(a)(3)(i).

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209 referred to as an RLD. In the electronic Orange Book, there will be a column for RLDs and a  
210 column for reference standards. In the printed version of the Orange Book, the RLDs and  
211 reference standards will be identified by specific symbols.

212  
213 Once an ANDA applicant chooses the RLD on which it intends to rely, the FD&C Act and FDA  
214 regulations prohibit the applicant from amending or supplementing its ANDA to change the  
215 RLD after the ANDA has been submitted.<sup>30</sup> An ANDA applicant that seeks to change its RLD  
216 must submit a new ANDA to obtain approval under section 505(j) of the FD&C Act.<sup>31</sup> We  
217 recommend that an ANDA applicant request withdrawal of the pending ANDA before seeking to  
218 change its RLD.

### **C. Reference Standard**

#### *1. Selection of a Reference Standard*

222 As discussed above, the FD&C Act requires an applicant to provide “information to show that  
223 the new drug is bioequivalent” to its RLD.<sup>32</sup> If bioequivalence is not self-evident, there are a  
224 variety of methods by which bioequivalence may be demonstrated, including in vivo studies (in  
225 human subjects), in vitro studies (conducted in a laboratory), or both.<sup>33</sup>

226  
227  
228  
229 A “reference standard” is the drug product selected by FDA that an applicant seeking approval of  
230 an ANDA must use in conducting an in vivo bioequivalence study required for approval of the  
231 ANDA.<sup>34</sup> To facilitate generic drug development, FDA generally selects a single reference  
232 standard that ANDA applicants must use in any in vivo testing conducted to support a  
233 demonstration of bioequivalence. FDA selects a single reference standard to ensure the greatest  
234 level of consistency between a generic drug and its RLD and among generic drugs. Ordinarily,  
235 the reference standard selected by FDA will be the RLD.<sup>35</sup> FDA usually selects as the reference  
236 standard the highest strength available for drug products with multiple approved strengths.<sup>36</sup> If

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<sup>30</sup> Section 505(j)(2)(D) of the FD&C Act; 21 CFR 314.96(c). We note that where an applicant has previously mistakenly identified the reference standard (described in detail in section III.C.) as the RLD on FDA Form 356h or elsewhere in its ANDA, the applicant may submit an amendment to a pending ANDA or a supplement to an approved ANDA to correct the information. FDA considers this error to be a deficiency related to identification of the appropriate listed drug as the RLD, rather than a change in the RLD itself. The cover letter for such a submission should clearly identify that the purpose of the submission is “Correction of RLD information.”

<sup>31</sup> Section 505(j)(2)(D)(i) of the FD&C Act. See also 21 CFR 314.96(c).

<sup>32</sup> Section 505(j)(2)(A)(iv) of the FD&C Act.

<sup>33</sup> 21 CFR 320.24.

<sup>34</sup> 21 CFR 314.3(b). We note that in vivo bioequivalence evidence is not required in all circumstances, see, e.g., 21 CFR 320.22 and 320.24(b)(6). When in vivo bioequivalence testing is required or an applicant otherwise seeks to support a demonstration of bioequivalence with in vivo data, such testing should be conducted with the drug product FDA selects as the reference standard.

<sup>35</sup> An ANDA applicant may use the authorized generic version of the RLD as the reference standard for purposes of conducting an in vivo bioequivalence study required for approval. See section 505(t) of the FD&C Act for additional information on authorized generics.

<sup>36</sup> See *Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule*, 81 FR 69619 (October 6, 2016). There may be instances in which the highest strength would not be the appropriate reference standard for testing in vivo bioequivalence. For example, FDA may select a different strength if testing at that different strength provides greater assurance of safety for the subject, is more feasible in terms of recruiting subjects who meet the study

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237 drug products are approved for multiple strengths but FDA has selected only one of the strengths  
238 as the reference standard, an applicant may use other approved strengths for testing other than in  
239 vivo bioequivalence testing (e.g., dissolution testing to support approval of those strengths not  
240 selected as a reference standard), if the use of such drug product in the particular testing is  
241 scientifically supported.

242  
243 Where FDA cannot select a drug product approved under section 505(c) of the FD&C Act as the  
244 reference standard (e.g., where the RLD has been withdrawn from sale for reasons other than  
245 safety and effectiveness), FDA generally will select a previously approved ANDA that referred  
246 to the RLD as the reference standard. If there are multiple approved generic products that  
247 referred to the RLD and have the same active ingredient, dosage form, route of administration,  
248 and strength, FDA usually will select the generic market leader, based on units sold, as the  
249 reference standard.

250  
251 As discussed above, even if FDA selects a reference standard that is a drug product other than  
252 the RLD for use in conducting in vivo bioequivalence studies, an ANDA applicant must  
253 demonstrate that its proposed generic drug meets the sameness requirements in section 505(j) of  
254 the FD&C Act and Agency regulations in relation to the RLD.

255  
256 Currently, a reference standard selected by FDA is indicated in the electronic version of the  
257 Orange Book with the word “RLD” in the “RLD” column, and in the paper version of the  
258 Orange Book with the “+” symbol, for drug products listed in the Active Sections. Starting in  
259 2017, FDA intends to modify the Orange Book to clarify which listed drugs are RLDs and which  
260 are reference standards. In the electronic Orange Book, there will be a column for RLDs and a  
261 column for reference standards. In the printed version of the Orange Book, the RLDs and  
262 reference standards will be identified by specific symbols.

### *2. Selection of a New Reference Standard*

263  
264  
265  
266 FDA may select a new reference standard when doing so will help to ensure that applications for  
267 generic drugs may be submitted and evaluated. In making a decision whether to select a new  
268 reference standard, FDA historically has considered, among other factors:

- 269
- 270 • Whether the listed drug that is the reference standard is no longer marketed;
  - 271 • Whether the listed drug that is the RLD has been withdrawn from sale for reasons of  
272 safety or effectiveness;<sup>37</sup>
  - 273 • Whether selecting a new reference standard would help to prevent a shortage of a  
274 particular drug product or category of drug products.<sup>38</sup>

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criteria, or is necessary to detect differences in effect. Further, applicants may submit a citizen petition to FDA requesting that FDA reconsider the strength selected for in vivo testing if, for example, clinical patterns of use of the drug product support use of a strength that differs from that selected by FDA as the reference standard.

<sup>37</sup> When FDA has made a determination that a listed drug has been withdrawn from sale for reasons of safety or effectiveness, the Agency will not select a new reference standard because the RLD will be removed from the Orange Book (and any ANDAs referencing that RLD will generally also be removed from the Orange Book).

<sup>38</sup> Executive Order 13588 on reducing prescription drug shortages was issued on October 21, 2011, and directs FDA to take steps to help prevent and reduce current and future disruptions in the supply of lifesaving drug products. For

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276 Now FDA also will consider selecting a new reference standard when the Agency determines  
277 that the quantity of the current reference standard in distribution is so limited that a potential  
278 ANDA applicant is not able to obtain a sufficient quantity for in vivo bioequivalence testing  
279 (even if the current reference standard is not in the Discontinued Section of the Orange Book).

280

281 When selecting a new reference standard, FDA generally selects a drug product that is  
282 therapeutically equivalent to the discontinued RLD and is the market leader based on units sold.  
283 In certain circumstances, FDA will consider additional factors in selecting a new reference  
284 standard. For example, as a practical matter, FDA may consider whether potential reference  
285 standards are approved for all the RLD strengths, which may make the development process  
286 more efficient, or whether a potential reference standard is approved for the particular strength  
287 that is recommended by FDA for use in in vivo bioequivalence studies in a product-specific  
288 guidance.<sup>39</sup>

289

### *3. Requesting Selection of a Reference Standard*

290

291 There are circumstances in which a potential ANDA applicant may ask FDA to select a reference  
292 standard. These circumstances include, for example, if FDA has not selected a reference  
293 standard, if a potential ANDA applicant believes a reference standard other than the one selected  
294 by FDA is appropriate, or if a reference standard is moved to the Discontinued Section and FDA  
295 has not selected a new reference standard for the same drug product. If there is no reference  
296 standard in the Active Section of the Orange Book for a drug product the applicant intends to  
297 duplicate, the potential applicant may submit controlled correspondence to FDA asking FDA to  
298 select a reference standard for that drug product. If there is a reference standard in the Active  
299 Section of the Orange Book but there are limited or no quantities of the reference standard in  
300 distribution, or a potential ANDA applicant believes a reference standard other than the one  
301 selected by FDA is appropriate, then the potential applicant may submit a citizen petition under  
302 21 CFR 10.25(a) and 10.30 to request that FDA select that different listed drug also as a  
303 reference standard. If the Agency selects a new reference standard, that product generally will  
304 remain the reference standard even if the original reference standard (e.g., the discontinued RLD)  
305 resumes marketing.

306

307 It is common practice for some stakeholders to refer to some generic drugs that are reference  
308 standards as *second RLDs*.<sup>40</sup> That description is not accurate, and has generated confusion  
309 regarding generic drug development and the role of the reference standard for both industry and  
310 the Agency. For example, FDA often receives citizen petitions requesting designation of a  
311 second RLD, when in fact the petition is requesting that FDA select a new reference standard. In  
312

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example, in June 2013, FDA removed Doxil as the reference standard for doxorubicin HCl liposome injection and selected Lipodox (ANDA 203263) as the reference standard. The shortage and continued unavailability of Doxil (NDA 050718), a lifesaving drug product for cancer treatment, meant that there existed no available reference standard against which to test a generic doxorubicin HCl liposome injection product, effectively shielding Doxil from further generic competition.

<sup>39</sup> See generally, guidance for industry on *Bioequivalence Recommendations for Specific Products* (June 2010).

<sup>40</sup> See the discussion above regarding designation of an additional RLD to ensure that a pharmaceutically equivalent drug product approved in an NDA is not shielded from generic competition.

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313 addition, ANDA applicants mistakenly have compared their proposed generic drugs to a  
314 reference standard to meet requirements for approval other than in vivo bioequivalence. While  
315 the reference standard is selected by FDA for the purpose of conducting any in vivo  
316 bioequivalence studies required for approval, an ANDA applicant must demonstrate that its  
317 proposed generic drug meets the sameness requirements in section 505(j) of the FD&C Act and  
318 Agency regulations in relation to the RLD. Accordingly, an ANDA's proposed labeling and  
319 formulation must be compared to the RLD, and not the reference standard, and the applicant  
320 must address any unexpired patents and exclusivity for the RLD as required.<sup>41</sup>

### **D. Basis of Submission**

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323 An ANDA applicant must identify in its application the basis of submission.<sup>42</sup>

#### *1. Basis of Submission for an ANDA for a Generic Drug that is the Same as its RLD*

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326  
327  
328 When an applicant submits an ANDA for a generic drug that is the same as its RLD, the basis of  
329 submission is the RLD. Accordingly, the name of the RLD, including dosage form and strength,  
330 and its application number<sup>43</sup> should be provided as the basis of submission on Form FDA 356h  
331 (i.e., the form that accompanies regulatory submissions by an applicant) and in the appropriate  
332 sections of the ANDA. If the reference standard selected by FDA for the drug product is not the  
333 RLD, an applicant should **not** identify the reference standard as the basis of submission on Form  
334 FDA 356h. However, the reference standard should be identified in the relevant sections of the  
335 ANDA that include information pertaining to bioequivalence, such as 1.12.11 Basis for  
336 submission statement (which statement provides information about the proposed generic drug  
337 broadly including bioequivalence, as well as other information), 2.7.1 Summary of  
338 Biopharmaceutical Studies and Associated Analytical Methods, 5.2 Tabular listing of all clinical  
339 studies, and 5.3.1 Reports of biopharmaceutical studies.<sup>44</sup> FDA guidance and technical documents  
340 related to ANDA formatting are maintained and updated on FDA's website.<sup>45</sup>

#### *2. Basis of Submission for First Petitioned ANDA*

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343  
344 When an applicant submits a petitioned ANDA,<sup>46</sup> the basis of submission is: (1) the RLD, which  
345 must be the same as the listed drug identified in the approved suitability petition; (2) a reference  
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<sup>41</sup> See, e.g., Section 505(j)(2)(B) of the FD&C Act; 21 CFR 314.94(a)(12).

<sup>42</sup> 21 CFR 314.94(a)(3).

<sup>43</sup> FDA previously has indicated that for drug products for which one NDA holder holds multiple approved NDAs for different strengths of the same drug product, it may be appropriate to accept an ANDA that references more than one NDA number. This promotes a more efficient use of the Agency's review resources. See guidance for industry on *Variations in Drug Products that May Be Included in a Single ANDA* (Dec. 1998).

<sup>44</sup> See Comprehensive Table of Contents Headings and Hierarchy, <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>, for electronic submissions.

<sup>45</sup> See, e.g., OGD's *ANDA Filing Checklist*, which provides technical information on how to organize an ANDA submission.

<sup>46</sup> See discussion of suitability petitions in the Background section of this guidance.

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347 to the suitability petition's FDA-assigned docket number; and (3) a copy of FDA's  
348 correspondence approving the suitability petition.<sup>47</sup> An applicant should identify on Form FDA  
349 356h both the RLD and the RLD's application number. In the basis of submission statement  
350 section (1.12.11) of the petitioned ANDA, in addition to identifying the RLD and its application  
351 number, the applicant should reference the FDA-assigned docket number for the suitability  
352 petition and include a copy of FDA's correspondence approving the suitability petition. Also,  
353 the RLD should generally be identified as the reference standard in that section.

354  
355 However, if after approval of a suitability petition and before approval of an ANDA submitted  
356 pursuant to the approved petition, a drug product is approved in an NDA for the change  
357 described in the petition, the suitability petition and the listed drug identified in the petition can  
358 no longer be the basis of submission, irrespective of whether FDA has withdrawn approval of the  
359 petition. Under these circumstances, an applicant seeking approval for a drug product with the  
360 change approved in the suitability petition must submit a new ANDA that identifies the drug  
361 product with the same active ingredient, dosage form, route of administration, and strength that  
362 has been approved under an NDA as the RLD and as its basis of submission and comply with  
363 applicable regulatory requirements.<sup>48</sup>

### *3. Basis of Submission for a Generic Drug that is the Same as a Drug Product Approved in a Petitioned ANDA*

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365  
366  
367  
368 When an ANDA applicant seeks approval of a generic drug that is a duplicate of a drug product  
369 in an approved petitioned ANDA (and for which the same drug has not been approved under  
370 section 505(c) of the FD&C Act), the basis of submission should be: (1) the RLD, which must be  
371 the same as the listed drug identified in the approved suitability petition, and RLD application  
372 number; (2) a reference to the suitability petition's FDA-assigned docket number; and (3) a copy  
373 of FDA's correspondence approving the suitability petition. The first petitioned ANDA  
374 approved should be used for and identified in the appropriate sections of a subsequent ANDA as  
375 the reference standard. However, the RLD for that subsequent ANDA remains the listed drug  
376 referenced in the approved suitability petition.

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<sup>47</sup> 21 CFR 314.94(a)(3)(i) and (iii).

<sup>48</sup> 21 CFR 314.93(f)(2). See also *Abbreviated New Drug Applications and 505(b)(2) Applications; Final Rule*, 81 FR 69621-69622 (October 6, 2016) (FDA finalized the requirement that an applicant with a pending ANDA subject to an approved suitability petition must change its RLD upon FDA approval of an NDA for the same drug product described in the approved suitability petition. This decision reflects the Agency's judgment that "considerations regarding an ANDA's limited reliance on an approved suitability petition are outweighed by the need for a clear determination of therapeutic equivalence for a generic drug product and protection of intellectual property rights accorded an NDA holder.")

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### 378 APPENDIX 1: QUICK REFERENCE

379

380 This appendix summarizes the concepts discussed in this guidance. We recommend that an  
381 ANDA applicant refer to the appropriate section of the guidance for more detailed information,  
382 as needed.

383

384 • The *reference listed drug (RLD)* for an ANDA is the drug product that the  
385 proposed generic drug is intended to duplicate and to which the ANDA applicant  
386 must refer in its ANDA. The RLD must be a listed drug approved under section  
387 505(c) of the FD&C Act based on a demonstration of safety and effectiveness.  
388 FDA identifies in the Orange Book listed drugs that are eligible to be RLDs.

389 Starting in 2017, FDA intends to modify the Orange Book to clarify which listed  
390 drugs are RLDs and which are reference standards, and to indicate which products  
391 in the Discontinued Section may be referred to as an RLD. In the electronic  
392 Orange Book, there will be a column for RLDs. In the printed version of the  
393 Orange Book, the RLDs will be identified by a specific symbol.

394

395 • In vivo bioequivalence studies needed to support an ANDA must be conducted  
396 using the drug product that FDA has selected as the *reference standard*. The  
397 reference standard may or may not be the same listed drug as the RLD. While the  
398 reference standard is selected by FDA for the purposes of conducting any in vivo  
399 bioequivalence testing required for approval, all other comparisons of the  
400 proposed generic drug to determine whether it meets the statutory requirements  
401 for approval under section 505(j) of the FD&C Act (e.g., sameness requirements)  
402 generally must be to the RLD. The reference standard for a drug product selected  
403 by FDA generally is identified in the Orange Book. In the electronic Orange  
404 Book, there will be a column for reference standards. In the printed version of the  
405 Orange Book, the reference standards will be identified by a specific symbol.

406

407 • If you mistakenly identify the reference standard as the RLD in your ANDA, you  
408 may submit an amendment to a pending ANDA or a supplement to an approved  
409 ANDA to correct the information. FDA considers this error to be a deficiency  
410 related to identification of the appropriate listed drug as the RLD, rather than a  
411 change in the RLD itself. The cover letter for such a submission should clearly  
412 identify that the purpose of the submission is “Correction of RLD information.”

413

414 • The *basis of submission* statement in an ANDA (e.g., in section 1.12.11 of the  
415 ANDA) and in Form FDA 356h (field 20) should include the RLD and the RLD  
416 application number. For a petitioned ANDA, the basis of submission statement in  
417 the ANDA (e.g., in section 1.12.11 of the ANDA) also should include a reference  
418 to the FDA-assigned docket number for the suitability petition and a copy of  
419 FDA’s correspondence approving the suitability petition. The reference standard,  
420 if it is different from the RLD, should be identified in the appropriate sections of  
421 the ANDA (e.g., sections 1.12.11, 2.7.1, 5.2, and 5.3.1).

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**TABLE: REFERENCING APPROVED DRUG PRODUCTS IN AN ANDA**

What drug product is the generic drug intended to be the same as?	RLD	Reference Standard	Identification of Basis of Submission in ANDA		Identification of reference standard in ANDA
			Form FDA 356h	ANDA	
ANDA for a generic drug that is the same as its RLD	The RLD must be a listed drug approved under section 505(c) of the FD&C Act.	Generally the RLD also is the reference standard.  If marketing of the RLD has been discontinued, the applicant should be able to find in the Orange Book the listed drug that FDA has selected as the reference standard for that drug product.	Fill in the name of RLD and its application number for field 20 on the form.	Identify the RLD and its application number in section 1.12.11.	Identify the reference standard in sections 1.12.11, 2.7.1, 5.2, and 5.3.1 of the ANDA.
ANDA for a generic drug for which a suitability petition has been approved	The listed drug identified in the approved suitability petition is the RLD.	Generally the listed drug identified in the approved suitability petition is the reference standard.  If marketing of such drug has been discontinued, the applicant should be able to find in the Orange Book the listed drug that FDA has selected as the reference standard for that drug product.	Fill in the name of RLD and its application number for field 20 on the form.	In section 1.12.11: <ul style="list-style-type: none"> <li>• Identify the RLD and its application number,</li> <li>• Identify the FDA-assigned docket number for the approved suitability petition, and</li> <li>• Include a copy of FDA’s correspondence approving the suitability petition</li> </ul>	Identify the reference standard in sections 1.12.11, 2.7.1, 5.2, and 5.3.1 of the ANDA.

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**TABLE: REFERENCING APPROVED DRUG PRODUCTS IN AN ANDA (cont'd)**

What drug product is the generic drug intended to be the same as?	RLD	Reference Standard	Identification of Basis of Submission in ANDA		Identification of reference standard in ANDA
			Form FDA 356h	ANDA	
ANDA for a generic drug that is the same as a drug product approved in a petitioned ANDA	The listed drug identified in the approved suitability petition is the RLD.	The drug product approved in the petitioned ANDA is the reference standard.  If marketing of such drug has been discontinued, the applicant should be able to find in the Orange Book the listed drug that FDA has selected as the reference standard for that drug product.	Fill in the name of RLD and its application number for field 20 on the form.	In section 1.12.11: <ul style="list-style-type: none"> <li>• Identify the RLD and its application number,</li> <li>• Identify the FDA-assigned docket number for the approved suitability petition, and</li> <li>• Include a copy of FDA's correspondence approving the suitability petition.</li> </ul>	Identify the reference standard in sections 1.12.11, 2.7.1, 5.2, and 5.3.1 of the ANDA.

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