

# Determining Whether to Submit an ANDA or a 505(b)(2) Application Guidance for Industry

## ***DRAFT GUIDANCE***

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For questions regarding this draft document, contact (CDER) Elizabeth Giaquinto Friedman 240-402-7930. If the contact is no longer available, please contact the Director of the Office of Generic Drug Policy, Office of Generic Drugs, CDER.

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

**October 2017  
Generics**

# Determining Whether to Submit an ANDA or a 505(b)(2) Application 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., 4<sup>th</sup> Floor  
Silver Spring, MD 20993-0002  
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353  
Email: [druginfo@fda.hhs.gov](mailto:druginfo@fda.hhs.gov)  
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**U.S. Department of Health and Human Services  
Food and Drug Administration  
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1                   **Determining Whether to Submit an ANDA or a 505(b)(2)**  
2                                   **Application**  
3                                   **Guidance for Industry<sup>1</sup>**  
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6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  
7 Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not  
8 binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the  
9 applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible  
10 for this guidance as listed on the title page.  
11

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15 **I. INTRODUCTION**  
16

17 This guidance is intended to serve as a foundational guidance to assist applicants in determining  
18 which one of the abbreviated approval pathways under the Federal Food, Drug, and Cosmetic  
19 Act (FD&C Act) is appropriate for the submission of a marketing application to FDA. Many  
20 potential drug product developers are familiar with neither the different abbreviated approval  
21 pathways for drug products under the FD&C Act — the abbreviated approval pathways  
22 described in section 505(j) and 505(b)(2) of the FD&C Act (21 U.S.C. 355(j) and 21 U.S.C.  
23 355(b)(2), respectively) — nor the types of data and information that are permitted to support  
24 approval under those pathways. In order to familiarize potential drug product developers with  
25 these abbreviated pathways, this guidance highlights criteria for submitting applications under  
26 the abbreviated approval pathways described in section 505(j) and 505(b)(2), identifies  
27 considerations to help potential applicants determine whether an application would be more  
28 appropriately submitted under section 505(j) or pursuant to section 505(b)(2) of the FD&C Act,  
29 and provides direction to potential applicants on requesting assistance from FDA in making this  
30 determination.  
31

32 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
33 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
34 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
35 the word *should* in Agency guidances means that something is suggested or recommended, but  
36 not required.  
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39 **II. BACKGROUND**  
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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 at the Food and Drug Administration.

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41 The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417)  
42 (Hatch-Waxman Amendments) added section 505(b)(2) and 505(j) to the FD&C Act, which  
43 describe abbreviated approval pathways under the FD&C Act for drug products regulated by the  
44 Agency. The Hatch-Waxman Amendments reflect Congress’s efforts to balance the need to  
45 “make available more low cost generic drugs by establishing a generic drug approval procedure”  
46 with new incentives for drug development in the form of exclusivities and patent term  
47 extensions.<sup>2</sup> With the passage of the Hatch-Waxman Amendments, the FD&C Act describes  
48 different routes for obtaining approval of two broad categories of drug applications: new drug  
49 applications (NDAs) and abbreviated new drug applications (ANDAs).<sup>3</sup>

50  
51 NDAs and ANDAs can be divided into the following four categories:<sup>4</sup>

- 52
- 53 (1) A “stand-alone NDA” is an application submitted under section 505(b)(1) and  
54 approved under section 505(c) of the FD&C Act that contains full reports of  
55 investigations of safety and effectiveness that were conducted by or for the  
56 applicant or for which the applicant has a right of reference or use.  
57
  - 58 (2) A 505(b)(2) application is an NDA submitted under section 505(b)(1) and  
59 approved under section 505(c) of the FD&C Act that contains full reports of  
60 investigations of safety and effectiveness, where at least some of the information  
61 required for approval comes from studies not conducted by or for the applicant  
62 and for which the applicant has not obtained a right of reference or use.<sup>5</sup>  
63
  - 64 (3) An ANDA is an application for a duplicate<sup>6</sup> of a previously approved drug  
65 product that was submitted and approved under section 505(j) of the FD&C Act.  
66 An ANDA relies on FDA’s finding that the previously approved drug product,  
67 i.e., the reference listed drug (RLD)<sup>7</sup>, is safe and effective. An ANDA generally

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<sup>2</sup> See H.R. Rep. No. 98-857, pt. 1, at 14-15 (1984), reprinted in 1984 U.S.C.C.A.N. 2647-2648.

<sup>3</sup> See section 505(b) and 505(j) of the FD&C Act. See generally 21 CFR part 314. FDA recently revised certain regulations in 21 CFR parts 314 and 320, and this guidance refers to those regulations as revised. See also 81 FR 69580 (October 6, 2016).

<sup>4</sup> See letter from Janet Woodcock to Katherine M. Sanzo, Jeffrey B. Chasnow, Stephen E. Lawton, and William R. Rakoczy (October 14, 2003), Docket Nos. FDA-2001-P-0369 (original Docket No. 2001P-0323/CP1 & C5), FDA-2002-P-0390 (original Docket No. 2002P-0447/CP1), and FDA-2003-P-0274 (original Docket No. 2003P-0408/CP1). (Please note that the docket numbers were changed in January 2008 after FDA transitioned to a new docketing system (Regulations.gov).)

<sup>5</sup> For more information on 505(b)(2) applications, see the draft guidance for industry *Applications Covered by Section 505(b)(2)*. When final, this guidance will represent the FDA’s current thinking on this topic. For the most recent version of a guidance, check the FDA Drugs guidance web page at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>.

<sup>6</sup> The term *duplicate* generally refers to a “drug product that has the same active ingredient(s), dosage form, strength, route of administration, and conditions of use as a listed drug.” See 54 FR 28872 at 28877 (July 10, 1989). However, the term *duplicate*, as used in this context, does not mean identical in all aspects to the listed drug.

<sup>7</sup> The *RLD* “is the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA.” 21 CFR 314.3(b). Because an ANDA applicant is relying upon FDA’s finding that the

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68 must contain information to show that the proposed generic product (1) is the  
69 same as the RLD with respect to the active ingredient(s), conditions of use, route  
70 of administration, dosage form, strength, and labeling (with certain permissible  
71 differences) and (2) is bioequivalent to the RLD. An ANDA may not be  
72 submitted if studies are necessary to establish the safety and effectiveness of the  
73 proposed product.  
74

- 75 (4) A petitioned ANDA is a type of ANDA for a drug product that differs from the  
76 RLD in its dosage form, route of administration, strength, or active ingredient (in  
77 a product with more than one active ingredient) and for which FDA has  
78 determined, in response to a petition submitted under section 505(j)(2)(C) of the  
79 FD&C Act (suitability petition), that studies are not necessary to establish the  
80 safety and effectiveness of the proposed drug product.  
81

82 This guidance focuses on those applications that can be submitted as ANDAs under section  
83 505(j) of the FD&C Act, petitioned ANDAs under section 505(j)(2)(C) of the FD&C Act, or  
84 NDAs pursuant to section 505(b)(2) of the FD&C Act. This guidance does not discuss stand-  
85 alone NDAs.  
86

87 A scientific premise underlying the Hatch-Waxman Amendments is that a drug product approved  
88 in an ANDA under section 505(j) of the FD&C Act is presumed to be therapeutically equivalent<sup>8</sup>  
89 to its RLD. Products classified as therapeutically equivalent can be substituted with the full  
90 expectation that the substituted product will produce the same clinical effect and safety profile as  
91 the prescribed product when administered to patients under the conditions specified in the  
92 labeling.<sup>9</sup> In contrast to an ANDA, a 505(b)(2) application allows greater flexibility as to the  
93 characteristics of the proposed product. A 505(b)(2) application will not necessarily be rated  
94 therapeutically equivalent to the listed drug it references upon approval.  
95

### **III. ABBREVIATED APPROVAL PATHWAYS**

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RLD is safe and effective, the RLD is a drug product approved under section 505(c) of the FD&C Act for which FDA has made a finding of safety and effectiveness. For more information on RLDs, see the draft guidance for industry *Referencing Approved Drug Products in ANDA Submissions*. When final, this guidance will represent the FDA's current thinking on this topic.

<sup>8</sup> See 21 CFR 314.3(b) (“Therapeutic equivalents are approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling.”). See also preface to *FDA’s Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) (pg. vii, 37th ed.), available at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf>.

<sup>9</sup> See preface to the Orange Book (pg. vii, 37th ed.).

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### **A. ANDAs<sup>10</sup>**

As discussed in section II of this guidance, section 505(j) of the FD&C Act, together with its implementing regulations, generally requires that an ANDA demonstrate that the proposed generic drug product and the applicable RLD are the same with respect to their active ingredient(s), dosage form, route of administration, strength, previously approved conditions of use, and labeling (with certain exceptions).<sup>11</sup> An ANDA must also include sufficient information (1) to demonstrate that the proposed product is bioequivalent to the RLD<sup>12</sup> and (2) to ensure the product's identity, strength, quality, and purity. Consistent with any statutory provisions related to the exclusivity of and patents listed for the RLD, FDA must approve an ANDA unless there is insufficient evidence that these criteria are met.<sup>13</sup> An ANDA relies on the Agency's finding of safety and effectiveness for an RLD and, as a result, that ANDA may be approved without submission of the same type and extent of information as is required for an NDA to establish the safety and efficacy of the proposed product.<sup>14</sup>

Also as discussed in section II above, an ANDA may contain certain types of differences from an RLD (e.g., a change approved in a suitability petition or other permissible differences, such as certain differences in inactive ingredients, labeling, or container closure systems), as long as investigations are not necessary to establish the safety or effectiveness of the drug product proposed in the ANDA.

### **B. 505(b)(2) Applications**

As discussed in section II above, an application submitted through the pathway described in section 505(b)(2) of the FD&C Act contains full reports of investigations of safety and effectiveness, where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use<sup>15</sup> (e.g., the Agency's finding of safety and/or effectiveness for a listed drug, published literature). A 505(b)(2) applicant may rely on FDA's finding of safety and/or effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration,

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<sup>10</sup> Please note that this guidance is intended to assist applicants deciding whether to submit an ANDA or a 505(b)(2) application but does not provide details on the content and format of or the submission process for an ANDA. For more information on the content and format of or the submission process for an ANDA, though, select the "Generics" heading on the FDA Drugs guidance web page. For information on the content and format of or the submission process for an NDA, select the "Clinical" and "Procedural" headings on the FDA Drugs guidance web page.

<sup>11</sup> See section 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94 and 21 CFR 314.127.

<sup>12</sup> See section 505(j)(2)(A)(iv) and 505(j)(4)(F) of the FD&C Act and 21 CFR 320.21(b).

<sup>13</sup> See section 505(j)(2)(A) and 505(j)(4) of the FD&C Act and 21 CFR 314.94, 314.105, and 314.127.

<sup>14</sup> See section 505(j)(2)(A) of the FD&C Act.

<sup>15</sup> See 21 CFR 314.3(b) ("Right of reference or use is the authority to rely upon, and otherwise use, an investigation for the purposes of obtaining approval of an NDA, including the ability to make available the underlying raw data from the investigation for FDA audit, if necessary.").

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130 strength, indication, conditions of use) in common with the listed drug.<sup>16</sup> The applicant, though,  
131 is expected to establish a *bridge* (e.g., by using comparative bioavailability data) between the  
132 proposed drug product and each listed drug that the applicant seeks to rely upon to demonstrate  
133 that reliance on the listed drug is scientifically justified. To the extent that the listed drug and the  
134 drug proposed in the 505(b)(2) application differ (e.g., a product with a different dosage form or  
135 a product that is intentionally more bioavailable than the listed drug), the 505(b)(2) application  
136 must include sufficient data to support those differences.<sup>17</sup> If FDA has approved one or more  
137 pharmaceutically equivalent products<sup>18</sup> in one or more NDAs before the date of the submission  
138 of the original 505(b)(2) application, the 505(b)(2) applicant must identify one such  
139 pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon but  
140 need not provide a scientific bridge to that product unless it is scientifically necessary to support  
141 approval.<sup>19</sup>

#### **IV. SUBMISSION THROUGH THE APPROPRIATE ABBREVIATED APPROVAL PATHWAY**

##### **A. Regulatory Considerations for ANDAs and 505(b)(2) Applications**

###### *1. Duplicates*

151 FDA generally will refuse to file a 505(b)(2) application for a drug that is a duplicate of a listed  
152 drug and eligible for approval under section 505(j) of the FD&C Act.<sup>20</sup>

154 If FDA approves a pharmaceutical equivalent to a proposed product before a 505(b)(2)  
155 application is *submitted*, such that the proposed product would be a duplicate of that  
156 pharmaceutically equivalent drug product and therefore eligible for approval under section 505(j)  
157 of the FD&C Act, FDA will refuse to file the application as a 505(b)(2) application. However, if  
158 FDA approves a duplicate drug product after a 505(b)(2) application is submitted but before the  
159 505(b)(2) application is approved, that application would remain eligible for approval as a  
160 505(b)(2) application, and FDA would not require the applicant of the pending 505(b)(2)  
161 application to withdraw the application and submit an ANDA.

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<sup>16</sup> A drug product in a 505(b)(2) application is not necessarily bioequivalent or therapeutically equivalent to the listed drug(s) relied upon.

<sup>17</sup> See 21 CFR 314.54(a). See also letter from Janet Woodcock to Katherine M. Sanzo, Jeffrey B. Chasnow, Stephen E. Lawton, and William R. Rakoczy (October 14, 2003), *supra* note 4.

<sup>18</sup> Generally, *pharmaceutical equivalents* are products that contain the same active ingredient(s), dosage form, route of administration, and strength. See 21 CFR 314.3.

<sup>19</sup> See 21 CFR 314.50(i)(1)(i)(C), 314.54(a)(1)(iii) and (vi) and 314.125(b)(19). See also 81 FR 69580 at 69620-21 (October 6, 2016).

<sup>20</sup> 21 CFR 314.101(d)(9) (noting that FDA may refuse to file an NDA if the “NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the [FD&C] Act.”).



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### ***2. Petitioned ANDAs***

As noted in section II of this guidance, certain differences between an RLD and a proposed generic drug product may be permitted in an ANDA if these differences are the subject of an approved suitability petition.<sup>21</sup> An applicant may submit a suitability petition to FDA requesting permission to submit an ANDA for a generic drug product that differs from an RLD in its route of administration, dosage form, or strength or that has one different active ingredient in a fixed-combination drug product.<sup>22</sup> An ANDA citing a suitability petition that has not been approved will not be received for review because the application lacks a legal basis for the submission.<sup>23</sup>

FDA will approve a suitability petition unless, among other things, (1) it determines that the safety and effectiveness of the proposed change from the RLD cannot be adequately evaluated without data from investigations that exceed what may be required for an ANDA<sup>24</sup> or (2) the petition is for a drug product for which a pharmaceutical equivalent has been approved in an NDA, including, for example, a 505(b)(2) application that referenced the same listed drug named in the suitability petition.<sup>25</sup> In the latter case, the ANDA applicant should instead refer to the approved pharmaceutical equivalent designated by the Agency as the RLD as the basis for its ANDA. After approval of an NDA for a drug product that is a pharmaceutical equivalent to the drug product described in the suitability petition, the approved suitability petition and listed drug described therein may no longer be used as the basis for an ANDA submission by applicants with pending ANDAs or by prospective ANDA applicants.<sup>26</sup> In this scenario, an applicant with a pending ANDA will be required to submit a new ANDA that both identifies the pharmaceutically equivalent product as the RLD and complies with applicable regulatory requirements.<sup>27</sup>

### ***3. Bundling***

In some circumstances, an applicant may seek approval for multiple drug products containing the same active ingredient(s) when some of these products would qualify for approval under the section 505(j) pathway and some would qualify for approval under the 505(b)(2) pathway. In these circumstances, FDA has permitted an applicant to submit a single 505(b)(2) application for all such multiple drug products that are permitted to be bundled in a single NDA.<sup>28</sup> For example,

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<sup>21</sup> See 21 CFR 314.93.

<sup>22</sup> See section 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93.

<sup>23</sup> See the guidance for industry *ANDA Submissions—Refuse-to-Receive Standards* (Rev. 2) (RTR Guidance) at 5-6.

<sup>24</sup> See section 505(j)(2)(A) and 505(j)(2)(C) of the FD&C Act and 21 CFR 314.93(e)(1)(i).

<sup>25</sup> 21 CFR 314.93(e)(1)(vi). See also 21 CFR 314.93(b).

<sup>26</sup> 21 CFR 314.93(f)(2).

<sup>27</sup> See *id.* See also 81 FR 69580 at 69621-22 (October 6, 2016).

<sup>28</sup> See the guidance for industry *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*.

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195 an applicant seeking approval for multiple strengths of a product, only some of which are listed  
196 in the Orange Book as RLDs, would not have to submit both an ANDA for the strengths listed in  
197 the Orange Book and a 505(b)(2) application for the new strengths; instead, the applicant may  
198 submit one 505(b)(2) application for all of the proposed strengths.

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### **B. Scientific Considerations for ANDAs and 505(b)(2) Applications**

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#### **1. Limited Confirmatory Studies**

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202 Although ANDAs and certain 505(b)(2) applications rely on the Agency’s finding of safety and  
203 effectiveness for a listed drug, any additional information that may support the approval of the  
204 proposed drug product may differ between these two submissions. The precise scope and type of  
205 additional information necessary for approval will vary and may be the subject of discussion  
206 between the applicant and FDA during the drug development process.<sup>29</sup>

207

208 In certain instances, limited confirmatory clinical studies may be acceptable in an ANDA if the  
209 purpose of those studies is not to *establish* safety and effectiveness.

210

211 In the preamble to the 1989 proposed rule to implement the Hatch-Waxman Amendments, in the  
212 context of suitability petitions FDA distinguished between limited confirmatory studies and data  
213 to establish safety and effectiveness as follows:

214

215 If preclinical or clinical data are needed to support safety, or if clinical data are  
216 needed to support the effectiveness of the requested change, then an ANDA is not  
217 appropriate for the proposed drug product.... However, under certain  
218 circumstances, data from limited confirmatory testing to show that the  
219 characteristics that make the proposed drug product different from the listed drug  
220 do not alter its safety and effectiveness may be accepted in a petition or as  
221 additional data to be included in an ANDA resulting from an approved  
222 petition.<sup>30, 31</sup>

223

224 If the safety and effectiveness of a proposed drug product must be established by investigations,  
225 these investigations go beyond the scope of a limited confirmatory study that may be submitted  
226 in an ANDA. We recommend that a prospective ANDA applicant considering submission of an  
227 application that may require data that could be considered outside of the scope of the ANDA  
228 pathway contact the Office of Generic Drugs (OGD) prior to submission of the application.<sup>32</sup>

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<sup>29</sup> See section V of this guidance for information about requesting assistance from FDA.

<sup>30</sup> 54 FR 28872 at 28880 (July 10, 1989).

<sup>31</sup> See also 57 FR 17950 at 17958 (April 28, 1992) (explaining that, in the context of suitability petitions, limited confirmatory studies “do not include animal or clinical studies whose information is necessary to show that the drug is safe or effective. Thus, FDA does not intend to permit petitioners to substitute limited confirmatory testing for clinical studies or otherwise circumvent NDA requirements.”).

<sup>32</sup> See section V of this guidance for information about requesting assistance from OGD.

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### 2. *Active Ingredient Sameness Evaluation*

As stated in sections II. and III.A of this guidance, section 505(j) of the FD&C Act generally requires that a proposed generic drug product demonstrate that it is the same as the RLD with respect to active ingredient(s).<sup>33</sup> If the active ingredient in an applicant’s proposed drug product cannot be demonstrated to be the same as the active ingredient in the RLD by using the information and data that may be submitted in connection with an ANDA, the drug product should not be submitted for approval in an ANDA.

FDA has broad discretion to determine whether an ANDA applicant has submitted information sufficient for the Agency to reasonably conclude that the proposed drug product’s active ingredient is the same as the active ingredient in the RLD.<sup>34</sup> That is, the statutory provisions outlining the contents of an ANDA do not describe the type or amount of information that an ANDA applicant must submit to demonstrate that the active ingredient in the generic drug product is the same as the active ingredient in the RLD. In addition, in the preamble to the final rule to implement the Hatch-Waxman Amendments, FDA specifically rejected the adoption of requirements that active ingredients “exhibit the same physical and chemical characteristics [as the RLD], that no additional residues or impurities can result from the different manufacture or synthesis process, and that the stereochemical characteristics and solid state forms of the drug have not been altered.”<sup>35</sup> Instead, FDA has adopted a more flexible approach.<sup>36</sup>

In some instances, current limitations of scientific understanding and technology may preclude approval of an ANDA with the data permitted for submission in an ANDA, including, for example, with respect to establishing active ingredient sameness of a given product. As scientific understanding and technology evolve, though, FDA may be able to receive, review, and approve ANDAs where it previously lacked the scientific basis to do so. We therefore recommend that a prospective ANDA applicant with questions about determining active ingredient sameness contact OGD prior to submission of the application.<sup>37</sup>

### 3. *Intentional Differences Between the Proposed Drug Product and the RLD*

#### a. *Differences in formulation*

Although section 505(j) of the FD&C Act generally requires that the active ingredient(s) in a proposed ANDA be the same as the active ingredient(s) in the RLD, certain differences in inactive ingredients are permissible. An ANDA must include information regarding the identity and quantity of all active and inactive ingredients of the proposed drug product (i.e., the

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<sup>33</sup> See section 505(j)(2)(A)(ii) and 505(j)(4)(C) of the FD&C Act.

<sup>34</sup> See generally *Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998).

<sup>35</sup> 57 FR 17950 at 17958-59 (April 28, 1992).

<sup>36</sup> *Id.* at 17959. See also letter from Janet Woodcock to J. Michael Nicholas (April 16, 2015), Docket No. FDA-2015-P-1050.

<sup>37</sup> See section V of this guidance for information about requesting assistance from OGD.

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269 formulation) and a characterization of any permitted differences between the formulations of the  
270 proposed drug product and the RLD, along with a justification demonstrating that the safety and  
271 effectiveness of the proposed drug product is not adversely affected by these differences.<sup>38</sup> For  
272 products for certain routes of administration, the types of changes to inactive ingredients that are  
273 permissible in an ANDA have been limited by regulation.<sup>39</sup> For example, in order to qualify for  
274 submission as an ANDA:

- 275
- 276 • Parenteral drug products generally must contain the same inactive ingredients and in the  
277 same concentrations as the RLD.<sup>40</sup> However, specific qualitative and quantitative  
278 changes from the RLD formulation are permitted in an ANDA for a parenteral drug  
279 product for certain inactive ingredients (i.e., preservatives, buffers, and antioxidants) that  
280 are considered *exception excipients*.<sup>41</sup> All other inactive ingredients in a proposed  
281 parenteral drug product must be qualitatively and quantitatively the same (Q1/Q2 same)<sup>42</sup>  
282 as the RLD.<sup>43</sup>
  - 283
  - 284 • Ophthalmic drug products generally should be Q1/Q2 same as the RLD with respect to  
285 all of their inactive ingredients.<sup>44</sup> As stated in 21 CFR 314.94(a)(9)(iv), though, an  
286 ANDA for an ophthalmic drug product may contain differences from the RLD with  
287 respect to certain inactive ingredients (i.e., preservatives, buffers, substances to adjust  
288 tonicity, or thickening agents), which are considered *exception excipients*.<sup>45</sup> For certain

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<sup>38</sup> 21 CFR 314.94(a)(9)(ii). See also 21 CFR 314.94(a)(5) for active ingredient identity and §314.94(a)(6) for active ingredient strengths.

<sup>39</sup> See 21 CFR 314.94(a)(9)(iii) and (iv).

<sup>40</sup> 21 CFR 314.94(a)(9)(iii).

<sup>41</sup> Id. (“However, an applicant may seek approval of a [parenteral] drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.”).

<sup>42</sup> See RTR Guidance at 8, n.46 (“[Q]uantitative sameness generally is interpreted by OGD to mean a concentration that is within 95-105% of the RLD concentration.”).

<sup>43</sup> See 21 CFR 314.94(a)(9)(iii). When an ANDA applicant seeks approval for a parenteral formulation that is the same as that previously marketed by the innovator, FDA has determined that, in appropriate circumstances, pursuant to 21 CFR 314.99(b), it may waive the requirement in the regulation that the inactive ingredients in a parenteral drug product approved under an ANDA be the same as those in the RLD (except for preservatives, buffers, and antioxidants), as long as the statutory requirement regarding safety of inactive ingredients has been met. See section 505(j)(4)(H) of the FD&C Act. In determining whether to grant such a waiver, the Agency considers, among other things, whether the previously marketed formulation was discontinued for reasons of safety or effectiveness. See, e.g., letter from Janet Woodcock to Steven H. Sklar and Peter O. Safir (November 7, 2012), Docket Nos. FDA-2011-P-0339 and FDA-2012-P-0507.

<sup>44</sup> See 21 CFR 314.94(a)(9)(iv).

<sup>45</sup> Id. (“However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, substance to adjust tonicity, or thickening agent provided that the applicant identifies and characterizes and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product, except that, in a product intended for ophthalmic use, an applicant may not change a buffer or substance to adjust tonicity for the purpose of claiming a therapeutic advantage over or difference from the listed

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289 ophthalmic drug products, however, FDA has determined that, as a scientific matter,  
290 qualitative or quantitative deviations from the RLD may raise a concern regarding safety  
291 or efficacy changes. In such cases, FDA may require an appropriate in vivo  
292 bioequivalence study or other studies.<sup>46</sup>

293  
294 • Otic drug products generally should be Q1/Q2 same as the RLD with respect to all of  
295 their inactive ingredients. Otic drug products may contain differences with respect to the  
296 exception excipients listed in 21 CFR 314.94(a)(9)(iv).<sup>47</sup>

297  
298 When an ANDA applicant seeks approval of a parenteral, ophthalmic, or otic drug product that  
299 differs from the RLD in its exception excipients, the applicant must identify and characterize the  
300 differences and provide information demonstrating that these differences do not affect the safety  
301 or efficacy of the proposed drug product.<sup>48</sup>

302  
303 An applicant should consider submitting a 505(b)(2) application if the proposed drug product  
304 contains changes to its formulation that are not permissible in an ANDA. For example, a  
305 proposed parenteral drug product that contains an additional inactive ingredient not present in the  
306 RLD that cannot be considered an exception excipient would not be permitted in an ANDA  
307 under the regulations at 21 CFR 314.94(a)(9)(iii) but may be submitted in a 505(b)(2)  
308 application. Similarly, a proposed drug product that contains a novel excipient, e.g., an excipient  
309 that has not been used in an FDA-approved drug product, the safety of which cannot be  
310 established without clinical testing, would also not be permitted in an ANDA but may be  
311 submitted in a 505(b)(2) application. We recommend that prospective ANDA applicants (1)  
312 consider both the ANDA regulatory requirements for formulations applicable to specific routes  
313 of administration and the data that would be scientifically necessary to support any permissible  
314 differences in inactive ingredients between the proposed product and the RLD and (2) contact  
315 OGD prior to submission of the application.<sup>49</sup>

316  
317 b. Differences in bioequivalence and/or bioavailability

318  
319 An ANDA must contain information to show that the proposed drug product is bioequivalent to  
320 the RLD.<sup>50</sup> A proposed drug product is bioequivalent to the RLD if

321  
322 the rate and extent of absorption of the [proposed] drug do not show a significant  
323 difference from the rate and extent of absorption of the [RLD] when administered

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drug, e.g., by using a balanced salt solution as a diluent as opposed to an isotonic saline solution, or by making a significant change in the pH or other change that may raise questions or irritability.”).

<sup>46</sup> See 21 CFR 320.21 and 21 CFR 320.22(b)(1).

<sup>47</sup> See RTR Guidance at 9.

<sup>48</sup> See 21 CFR 314.94(a)(9)(iii) and (iv).

<sup>49</sup> See section V of this guidance for information about requesting assistance from OGD.

<sup>50</sup> Section 505(j)(2)(a)(iv) and 505(j)(4)(F) of the FD&C Act and 21 CFR 314.94(a)(7)(i).

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324 at the same molar dose of the therapeutic ingredient under similar experimental  
325 conditions in either a single dose or multiple doses.<sup>51</sup>

326

327 Similarly, the definition of *bioequivalence* in the regulations states, in part, that

328

329 [w]here there is an intentional difference in rate (e.g., in certain extended-release  
330 dosage forms), certain pharmaceutical equivalents or alternatives may be  
331 considered bioequivalent if there is no significant difference in the extent to which  
332 the active ingredient or moiety from each product becomes available at the site of  
333 drug action.<sup>52</sup>

334

335 An application for a proposed drug product where the rate and/or extent of absorption exceed, or  
336 are otherwise different from, the 505(j) standards for bioequivalence may be submitted under the  
337 505(b)(2) pathway and may require studies to show the safety and efficacy of the proposed  
338 product at the different rate and/or extent of delivery.<sup>53</sup> However, FDA generally will not file a  
339 505(b)(2) application for a drug product

340

341 whose only difference from a listed drug is that: (1) [t]he extent to which its  
342 active ingredient(s) is absorbed or otherwise made available to the site of action is  
343 less than that of the listed drug; or (2) [t]he rate at which its active ingredient(s) is  
344 absorbed or otherwise made available to the site of action is unintentionally less  
345 than that of the listed drug.<sup>54</sup>

346

347 Therefore, a 505(b)(2) application is not appropriate for a drug product that should have been  
348 submitted under the ANDA pathway but failed to meet all of the 505(j) standards (e.g., the  
349 proposed drug product is a duplicate of a listed drug but is unintentionally less bioavailable and  
350 fails to demonstrate bioequivalence to the listed drug). Prospective ANDA applicants should  
351 contact OGD to discuss any differences in bioequivalence and bioavailability prior to submission  
352 of the application.<sup>55</sup>

353

354 c. Differences in conditions of use

355

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<sup>51</sup> Section 505(j)(8)(B)(i) of the FD&C Act. See also 21 CFR 314.3(b).

<sup>52</sup> 21 CFR 314.3(b).

<sup>53</sup> See 80 FR 6802 at 6855-56 (February 6, 2015) (“However, there are circumstances in which a proposed drug product that is pharmaceutically equivalent to a listed drug (*i.e.*, drug products in the same dosage form and route(s) of administration that contain the same amount of the same active drug ingredient and that meet other applicable standards) is not eligible for approval as an ANDA and must be submitted as an NDA. For example, a proposed extended-release drug product may intentionally differ in its pharmacokinetic profile from a listed drug that is also an extended-release drug product such that the proposed product cannot meet the bioequivalence requirement for ANDAs.”).

<sup>54</sup> 21 CFR 314.54(b)(1) and (2).

<sup>55</sup> See section V of this guidance for information about requesting assistance from OGD.

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356 An application submitted under section 505(j) of the FD&C Act must include a statement that  
357 the conditions of use prescribed, recommended, or suggested in the labeling for the proposed  
358 drug product have been previously approved for the RLD.<sup>56</sup> If an applicant has made changes to  
359 a proposed 505(j) drug product such that the proposed labeling of the drug product does not  
360 reflect the previously approved conditions of use (e.g., the proposed drug product has added a  
361 new indication), the application could not be approved as an ANDA.<sup>57</sup> However, FDA will not  
362 refuse to approve an ANDA whose labeling excludes conditions of use approved for the RLD  
363 that may be omitted from the proposed ANDA labeling because of patents or exclusivity.<sup>58</sup> We  
364 recommend that prospective ANDA applicants considering a change that could be construed as a  
365 change to the conditions of use of the RLD contact OGD before submission.<sup>59</sup>

### 4. Other Differences

368  
369 As noted in this guidance, some differences are permitted between an RLD and a proposed drug  
370 product in an ANDA. However, drug products that differ considerably from the RLD are  
371 generally not candidates for the section 505(j) pathway. In assessing whether differences  
372 between a proposed generic drug product and the RLD would necessitate additional data or  
373 information to establish the safety or efficacy of the proposed drug product, FDA examines not  
374 only individual differences between the products, but also the combined effects of those  
375 differences. If differences between a proposed product and its RLD may require submission of  
376 data or information that could be considered beyond the scope of studies that can be reviewed in  
377 an ANDA, a prospective ANDA applicant should contact OGD prior to submission.<sup>60</sup>

#### a. Device Constituents

378  
379  
380  
381 FDA recognizes that an applicant of a proposed generic drug device combination product may  
382 choose to develop a device constituent that has some differences in design from the RLD. We  
383 recommend that prospective applicants intending to submit an ANDA for a proposed  
384 combination product that includes both a drug constituent part and a delivery device constituent  
385 part review the draft guidance for industry *Comparative Analyses and Related Comparative Use*  
386 *Human Factors Studies for a Drug-Device Combination Product Submitted in an ANDA*.<sup>61</sup>

#### b. Labeling

387  
388  
389  
390 An ANDA must contain

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<sup>56</sup> 21 CFR 314.94(a)(4)(i).

<sup>57</sup> 21 CFR 314.127(a)(2).

<sup>58</sup> 21 CFR 314.92(a)(1).

<sup>59</sup> See section V of this guidance for information about requesting assistance from OGD.

<sup>60</sup> Id.

<sup>61</sup> This draft guidance, when finalized, will represent the Agency's current thinking on this topic. We also recommend that a prospective ANDA applicant with questions about proposed generic drug-device combination products contact OGD prior to submission. See section V of this guidance for information about requesting assistance from OGD.

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391  
392 information to show that the labeling proposed for the new drug is the same as the  
393 labeling approved for the [RLD]...except for changes required because of  
394 differences approved under a [suitability petition]... or because the new drug and  
395 the [RLD] are produced or distributed by different manufacturers.<sup>62</sup>  
396

397 The regulations at 21 CFR 314.94(a)(8)(iv) recognize that certain differences in labeling between  
398 generic drug products and RLDs (e.g., differences in the products' expiration dates, formulation,  
399 bioavailability, or pharmacokinetics; labeling revisions made to comply with current FDA  
400 labeling guidelines or guidance; or the omission of an indication or other aspect of labeling  
401 protected by patent or exclusivity) may be appropriate because the generic drug product and the  
402 RLD are produced or distributed by different manufacturers.<sup>63</sup> Though the regulations indicate  
403 that these identified examples are not the only acceptable differences in labeling between the  
404 generic drug product and the RLD, certain differences in labeling will determine whether the  
405 proposed drug product should be submitted in an ANDA or a 505(b)(2) application. For  
406 example, an ANDA is not appropriate if the proposed drug product would have a new indication  
407 or a new dosing regimen as compared to the RLD (e.g., a proposed product would be  
408 administered once daily even though the RLD is labeled for administration twice daily).  
409

410 Differences in labeling between the proposed generic product and the RLD must not render the  
411 proposed drug product less safe or effective than the RLD.<sup>64</sup> If the differences between the  
412 products are such that they would require investigations to establish the safety or effectiveness of  
413 the proposed product or necessitate such significant labeling differences that the labeling no  
414 longer satisfies the "same" labeling requirement, the proposed drug product should be submitted  
415 under section 505(b) of the FD&C Act.  
416

### **V. REQUESTING ASSISTANCE FROM FDA**

417  
418 If an applicant is developing a product that is intended to have the same active ingredient,  
419 conditions of use, route of administration, dosage form, strength, and (with certain permissible  
420 differences) labeling as an RLD and has questions about qualification as an ANDA, the applicant  
421  
422

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<sup>62</sup> Section 505(j)(2)(A)(v) of the FD&C Act. See also 21 CFR 314.94(a)(8)(iv) (requiring that the labeling for a proposed generic product "be the same as the labeling approved for the [RLD], except for changes required because of differences approved under a [suitability petition]... or because the drug product and the [RLD] are produced or distributed by different manufacturers." Such permitted differences in labeling include an "omission of an indication or other aspect of labeling protected by patent or accorded exclusivity under section 505(j)(5)(F) of the [FD&C] Act.").

<sup>63</sup> 21 CFR 314.94(a)(8)(iv). See also 21 CFR 314.127(a)(7).

<sup>64</sup> For example, in reference to labeling carve-outs as discussed in section IV.B.3.c of this guidance, FDA considers whether an ANDA that omits the protected information from its labeling would be rendered less safe or effective than the RLD for its remaining non-protected conditions of use. See 21 CFR 314.127(a)(7).



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423 may submit controlled correspondence<sup>65</sup> to or request a pre-ANDA meeting with the Office of  
424 Generic Drugs (OGD). Controlled correspondence is appropriate if an applicant has a specific  
425 and targeted inquiry about the generic drug development process. A pre-ANDA meeting is  
426 appropriate for a prospective applicant seeking a dialogue with the Agency on a particular matter  
427 that would fall outside the scope of controlled correspondence. Requests for pre-ANDA  
428 meetings should be submitted to [GenericDrugs@fda.hhs.gov](mailto:GenericDrugs@fda.hhs.gov).

429  
430 If an applicant is developing a product that has a different active ingredient, conditions of use,  
431 route of administration, dosage form, strength, or labeling than a listed drug and/or is proposing a  
432 clinical study program and has questions about submission of an application through the  
433 505(b)(2) pathway, the applicant should contact the appropriate Office of New Drugs review  
434 division for assistance.<sup>66</sup>  
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<sup>65</sup> See the guidance for industry *Controlled Correspondence Related to Generic Drug Development* for information on the types of inquiries accepted as controlled correspondence and on how to submit controlled correspondence to OGD.

<sup>66</sup> For more information on contacting the appropriate Office of New Drugs review division for a possible 505(b)(2) application, see FDA's "Enhanced Communication" web page at <http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm327281.htm>.