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# Considerations for Waiver Requests for pH Adjusters in Generic Drug Products Intended for Parenteral, Ophthalmic, or Otic Use 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## *DRAFT GUIDANCE*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)**

**April 2022  
Generic Drugs**

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

**April 2022  
Generic Drugs**

*Contains Nonbinding Recommendations*

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1 **Considerations for Waiver Requests for pH Adjusters in Generic**  
2 **Drug Products Intended for Parenteral, Ophthalmic, or Otic Use**  
3 **Guidance for Industry<sup>1</sup>**  
4

5  
6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  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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13  
14  
15 **I. INTRODUCTION**  
16

17 This guidance describes how FDA (the Agency, or we) intends to evaluate a request for a waiver,  
18 with regard to a pH adjuster, under 21 CFR 314.99(b) (hereinafter waiver) of the requirement in  
19 21 CFR 314.94(a)(9)(iii) and (iv) that a drug product intended for parenteral, ophthalmic, or otic  
20 use generally “must contain the same inactive ingredients and in the same concentration as the  
21 reference listed drug identified by the applicant.” This guidance also provides recommendations  
22 regarding the timing and process for requesting such a waiver of the requirement in §  
23 314.94(a)(9)(iii) and (iv) (waiver request).  
24

25 This guidance is intended to assist abbreviated new drug application (ANDA)<sup>2</sup> applicants that  
26 reference a reference listed drug (RLD) intended for parenteral, ophthalmic, or otic use but are  
27 seeking approval of a drug that is qualitatively (Q1) different or quantitatively (Q2) different<sup>3</sup>  
28 from the RLD with respect to a pH adjuster(s).<sup>4</sup> This guidance is intended to identify the type of  
29 information FDA may generally consider in evaluating a waiver request for pH adjusters in  
30 generic drug products intended for parenteral, ophthalmic, or otic use and provide  
31 recommendations to ANDA applicants regarding the submission and content of such a waiver  
32 request.  
33

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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.

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

<sup>3</sup> OGD interprets *quantitative sameness* to mean a concentration that is within 95-105% of the reference listed drug concentration. That is, sameness as discussed herein does not suggest an exact value, but rather a range of values.

<sup>4</sup> There may be circumstances where a proposed difference in pH adjuster is not acceptable in an ANDA. Examples of such circumstances are discussed further in section III.B. below.

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34 The recommendations in this guidance are limited to inactive ingredients in ANDAs that adjust  
35 the pH of a drug product intended for parenteral, ophthalmic, or otic use, and do not apply to  
36 other inactive ingredients.<sup>5</sup>

37  
38 The contents of this document do not have the force and effect of law and are not meant to bind  
39 the public in any way, unless specifically incorporated into a contract. This document is intended  
40 only to provide clarity to the public regarding existing requirements under the law. FDA  
41 guidance documents, including this guidance, should be viewed only as recommendations, unless  
42 specific regulatory or statutory requirements are cited. The use of the word should in FDA  
43 guidance means that something is suggested or recommended, but not required.

44  
45

## **46 II. BACKGROUND**

47

48 The Drug Price Competition and Patent Restoration Act of 1984, commonly referred to as the  
49 “Hatch-Waxman Amendments,” created a statutory ANDA pathway by amending section 505 of  
50 the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355).<sup>6</sup> To obtain approval,  
51 the ANDA applicant generally must show, among other things, that the proposed generic drug  
52 product (1) has the same active ingredient(s), dosage form, route of administration, strength,  
53 conditions of use, and, with certain exceptions, labeling as the RLD; and (2) is bioequivalent to  
54 the RLD.<sup>7</sup>

55

### **56 A. Statutory and Regulatory Provisions Regarding Inactive Ingredients in ANDAs**

57

58 The FD&C Act does not require an ANDA product to have the same inactive ingredients as the  
59 RLD.<sup>8</sup> Section 505(j)(4)(H) of the FD&C Act does, however, state that an ANDA shall not be  
60 approved:

61

62 . . . if information submitted in the application or any other information available to the  
63 Secretary shows (i) the inactive ingredients of the drug are unsafe for use under the  
64 conditions prescribed, recommended, or suggested in the labeling proposed for the drug,  
65 or (ii) the composition of the drug is unsafe under such conditions because of the type or  
66 quantity of inactive ingredients included or the manner in which the inactive ingredients  
67 are included.<sup>9</sup>

68

69 The Agency has interpreted section 505(j)(4)(H) of the FD&C Act as permitting the Agency to  
70 deny approval of an ANDA “if there is a reasonable basis to conclude that its inactive ingredients  
71 or composition raise serious questions about the drug’s safety.”<sup>10</sup> In its implementing

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<sup>5</sup> The scientific principles described in this draft guidance may be relevant, in certain circumstances, to requests to use an in vitro approach to demonstrate bioequivalence (BE) for a proposed generic product intended for parenteral, ophthalmic, or otic use that is not Q1 or Q2 the same as the RLD. FDA encourages an applicant who proposes such a product that is not Q1 or Q2 the same as the RLD with respect to a pH adjuster(s), to contact the Agency to discuss its proposed approach to establish BE for its proposed drug product.

<sup>6</sup> Public Law 98-417 (Sept. 24, 1984).

<sup>7</sup> See generally, 21 CFR 314.94(a).

<sup>8</sup> See section 505(j)(2)(A) of the FD&C Act (setting forth the required contents of an ANDA).

<sup>9</sup> Section 505(j)(4)(H) of the FD&C Act.

<sup>10</sup> 21 CFR 314.127(a)(8)(ii); 54 FR 28871 at 28903 (July 10, 1989).

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72 regulations, FDA explicitly noted that “FDA may identify changes in inactive ingredients that  
73 may adversely affect a drug product’s safety or efficacy” based on the Agency’s “experience  
74 with reviewing inactive ingredients and other information available to it.”<sup>11</sup> In its regulations, the  
75 Agency has also provided non-exhaustive examples of changes in inactive ingredients in  
76 proposed generic drug products that may raise serious questions of safety,<sup>12</sup> including, for  
77 example:

- 78
- 79 • A change in an inactive ingredient so that the product does not comply with an  
80 official compendium;<sup>13</sup>
- 81
- 82 • A change in composition to include an inactive ingredient that has not been  
83 previously approved in a drug product for human use by the same route of  
84 administration;<sup>14</sup>
- 85
- 86 • A change in the composition of a parenteral drug product to include an inactive  
87 ingredient that has not been previously approved in a parenteral drug product;<sup>15</sup>
- 88
- 89 • A change in composition of a drug product for ophthalmic use to include an inactive  
90 ingredient that has not been previously approved in a drug for ophthalmic use;<sup>16</sup> and  
91
- 92 • A change in composition to include a significantly greater content of one or more  
93 inactive ingredients than previously used in the drug product.<sup>17</sup>
- 94

95 The regulations at § 314.94(a)(9)(iii) and (iv), with parallel provisions in the approval  
96 regulations at 21 CFR 314.127(a)(8)(ii)(B) and (C), further specify that FDA will consider an  
97 inactive ingredient in, or the composition of, a generic drug product intended for parenteral,  
98 ophthalmic, or otic use to be unsafe and will refuse to approve the ANDA unless the generic  
99 drug product contains the same inactive ingredients (with certain listed exceptions) in the same  
100 concentration as the RLD.<sup>18</sup> These regulations also identify permissible differences in certain  
101 inactive ingredients for drug products intended for parenteral, ophthalmic, or otic use, commonly  
102 referred to as “exception excipients,” if the ANDA contains sufficient information to  
103 demonstrate that any differences do not affect the safety or efficacy of the drug product; for  
104 example:

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<sup>11</sup> 21 CFR 314.127(a)(8)(ii)(A).

<sup>12</sup> See 54 FR 28871 at 28902 (discussing FDA’s interpretation of section 505(j)(3)(H) (now 505(j)(4)(H)) of the FD&C Act in the context of proposed rule 314.127 on the refusal to approve ANDAs).

<sup>13</sup> 21 CFR 314.127(a)(8)(ii)(A)(1).

<sup>14</sup> 21 CFR 314.127(a)(8)(ii)(A)(2).

<sup>15</sup> 21 CFR 314.127(a)(8)(ii)(A)(3).

<sup>16</sup> 21 CFR 314.127(a)(8)(ii)(A)(4).

<sup>17</sup> 21 CFR 314.127(a)(8)(ii)(A)(6).

<sup>18</sup> In evaluating drug product formulation and inactive ingredients, an ANDA applicant should compare its proposed generic drug to the RLD’s formulation, not the formulation of the reference standard (where the reference standard is not the RLD). See FDA guidance for industry *Referencing Approved Drug Products in ANDA Submissions* (October 2020). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

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- 106 • Drug products intended for parenteral use generally must contain the same inactive  
107 ingredients in the same concentration as the RLD; however, an applicant may seek  
108 approval of a drug product intended for parenteral use that differs from the RLD in  
109 preservative, buffer, or antioxidant provided that the applicant identifies and characterizes  
110 the differences and provides information demonstrating that the differences do not affect  
111 the safety or efficacy of the proposed drug product.<sup>19</sup>  
112
- 113 • Drug products intended for ophthalmic or otic use generally must contain the same  
114 inactive ingredients in the same concentration as the RLD; however, an applicant may  
115 seek approval for a drug product intended for ophthalmic or otic use that differs from the  
116 RLD in preservative, buffer, substance to adjust tonicity, or thickening agent provided  
117 that the applicant identifies and characterizes the differences and provides information  
118 demonstrating that the differences do not affect the safety or efficacy of the proposed  
119 drug product.<sup>20</sup>  
120

121 When proposing these regulations, the Agency provided a brief discussion for its reasoning in  
122 implementing the inactive ingredient requirements for drug products intended for parenteral,  
123 ophthalmic, or otic use:

124 [E]ach parenteral, ophthalmic, and otic drug product represents an individual  
125 pharmaceutical system with its own characteristics and requirements. In the formulation  
126 of parenteral drug products, certain added substances are used to maintain solubility,  
127 stability, sterility, and to increase patient comfort (i.e., by adjusting toxicity[sic] and  
128 reducing tissue irritation). Added substances selected for parenteral drug products *must*  
129 *be known to be of the highest quality, must be known to not interfere with the therapeutic*  
130 *effectiveness of the product and must be known to be nontoxic in the quantities used.* The  
131 sensitivity of inactive ingredients in parenteral drug products is reflected in regulations  
132 under 21 CFR 201.100 which require that certain added substances and their  
133 concentrations be listed on the label of the product. Similarly, added substances are used  
134 in the formulation of products intended for ophthalmic and otic use such as buffers,  
135 antimicrobial preservatives, chemicals to adjust toxicity [sic], and thickening agents.<sup>21</sup>  
136  
137

### **B. Waiver of Certain Regulatory Requirements for ANDAs**

138  
139  
140 When FDA updated its new drug regulations in the 1980s, the Agency promulgated a waiver  
141 provision “intended to give applicants flexibility to seek alternative ways of complying with the  
142 statutory standards for drug approval.”<sup>22</sup> FDA has since codified a waiver provision applicable to  
143 ANDAs at 21 CFR 314.99(b),<sup>23</sup> under which “an applicant may ask FDA to waive under this

<sup>19</sup> See 21 CFR 314.94(a)(9)(iii); see also 21 CFR 314.127(a)(8)(ii)(B).

<sup>20</sup> See 21 CFR 314.94(a)(9)(iv); see also 21 CFR 314.127(a)(8)(ii)(C). The regulations also specify that for products 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 RLD. See 21 CFR 314.94(a)(9)(iv).

<sup>21</sup> See 54 FR 28872 at 28883 (July 10, 1989) (emphasis added). Both references to “adjusting toxicity” appear to be an inadvertent error for “adjusting tonicity.”

<sup>22</sup> See 47 FR 46622 at 46637-38 (Oct. 19, 1982).

<sup>23</sup> See 54 FR 28872 at 28889 (Jul. 10, 1989) (proposing “to retain the current requirement under § 314.90 under which an applicant may obtain a waiver of requirements for the submission of information in an application. The

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144 section any requirement that applies to the applicant under 314.92 through 314.99.” As described  
145 in § 314.99(b), the applicant must comply with the requirements for a waiver under 21 CFR  
146 314.90 and FDA may grant a waiver if it finds one of the following:

- 147
- 148 (1) The applicant’s compliance with the requirement is unnecessary for the agency to  
149 evaluate the [A]NDA or compliance cannot be achieved;
- 150
- 151 (2) The applicant’s alternative submission satisfies the requirement; or
- 152
- 153 (3) The applicant’s submission otherwise justifies a waiver.<sup>24</sup>
- 154

155 Even if FDA grants a waiver of a requirement in § 314.92 through § 314.99 in a particular  
156 application, the application still must meet all applicable statutory requirements for approval.<sup>25</sup>  
157 If FDA grants the applicant’s waiver request with respect to a requirement under § 314.92  
158 through § 314.99, the waived requirement will not constitute a basis for refusal to approve an  
159 ANDA under § 314.127.<sup>26</sup>

160

161

### 162 **III. WAIVERS FOR pH ADJUSTERS IN GENERIC DRUGS INTENDED FOR** 163 **PARENTERAL, OPHTHALMIC, OR OTIC USE MAY BE APPROPRIATE IN** 164 **CERTAIN CIRCUMSTANCES**

165

166 Over time there has been increased interest in and questions about waivers of the applicable  
167 inactive ingredient requirements for pH adjusters in ANDAs. FDA’s current thinking is that pH  
168 adjusters function in such a way that, in some circumstances, a waiver of the inactive ingredient  
169 requirements in § 314.94(a)(9)(iii)-(iv) for a pH adjuster in a generic drug product intended for  
170 parenteral, ophthalmic, or otic use may be appropriate. In particular, how pH adjusters function  
171 or react in some formulations support the possibility that there may be circumstances where  
172 certain differences in pH adjusters in an ANDA as compared to the RLD may be scientifically  
173 appropriate and acceptable in an ANDA, as described in more detail below.

174

175 Accordingly, FDA believes that permitting such differences to pH adjusters through a waiver  
176 under § 314.99(b), as appropriate, is one way the waiver provision may enable flexibility in how  
177 a particular applicant meets the statutory standards for approval. Determining whether a  
178 particular difference in pH adjuster as compared to the RLD is scientifically acceptable and

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applicable sections are those set forth under new proposed Subpart C. FDA may not, however, waive statutory requirements”).

<sup>24</sup> See 21 CFR 314.99(b) (citing 21 CFR 314.90(b)).

<sup>25</sup> For example, when an ANDA applicant seeks approval for a parenteral formulation that is the same as that previously (but not currently) marketed for the RLD, 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. FDA2011-P-0339 and FDA-2012-P-0507.

<sup>26</sup> See 21 CFR 314.99(b).



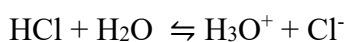
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179 appropriate in an ANDA is a fact-specific assessment within the context of a specific application  
180 and a specific § 314.99(b) waiver request. As noted in the preceding section, an application for  
181 which FDA grants a waiver must still meet all applicable requirements for approval.

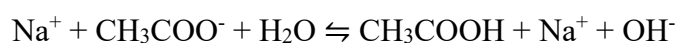
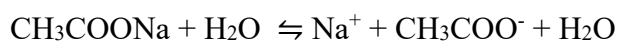
### 182 183 A. The Role of pH Adjusters 184

185 The primary function of a pH adjuster, which is commonly an acid or base, is to change the  
186 equilibrium concentration of hydronium ions in solution (i.e., the pH). In general, the greater the  
187 concentration of hydronium ions in solution, the lower the pH value, which is measured on a  
188 logarithmic scale. For example, in an aqueous solution (H<sub>2</sub>O), the balance of hydronium ions  
189 (H<sub>3</sub>O<sup>+</sup>) and hydroxide ions (OH<sup>-</sup>) determines whether the pH of the solution is acidic ([H<sub>3</sub>O<sup>+</sup>] >  
190 [OH<sup>-</sup>]), basic ([H<sub>3</sub>O<sup>+</sup>] < [OH<sup>-</sup>]), or neutral ([H<sub>3</sub>O<sup>+</sup>] = [OH<sup>-</sup>]). As the pH adjuster role is to change  
191 the equilibrium concentration of hydronium ions in solution, the pH value is routinely used as a  
192 surrogate to control the amount of pH adjuster added. For example, the amount of hydrochloric  
193 acid (HCl) pH adjuster added to an aqueous solution generates an equivalent amount of  
194 hydronium and chloride ions. Therefore, a measure of the hydronium ion concentration (i.e., pH)  
195 is correlated to the amount of HCl added:



198  
199 In FDA's experience reviewing applications for drug products intended for parenteral,  
200 ophthalmic, or otic use, pH adjusters are typically used on an as-needed basis to achieve a  
201 specified pH range in the drug product. These drug products often express the quantity of pH  
202 adjuster used as *quantum satis* (q.s.), which means the quantity added is as much or as little  
203 (which may be none) as necessary to achieve a specified pH range for any given batch of drug  
204 product. Thus, this specified pH range of the drug product is the primary aim, and the amount of  
205 pH adjuster used to achieve the pH of the drug product is adjusted accordingly.

206  
207 In cases where a formulation contains other ingredients that may act as a buffer, pH adjusters  
208 react with and may function as part of the buffer system to control the pH. In general, a buffer  
209 system is composed of a weak acid that is in equilibrium with its conjugate base, or vice versa.  
210 A buffer can be created in various ways; for example, by adding defined ratios of the weak acid  
211 and conjugate base or by adding a pH adjuster to convert some of the weak acid into the  
212 conjugate base. Thus, a pH adjuster can become an indistinguishable part of the buffer. For  
213 example, an acetic acid (CH<sub>3</sub>COOH) sodium acetate (CH<sub>3</sub>COONa) buffer may be created by  
214 mixing a ratio of these two ingredients in solution or by adding a sodium hydroxide (NaOH) pH  
215 adjuster to acetic acid. In solution, the buffer component species (i.e., acetic acid and sodium  
216 acetate) and pH adjuster (i.e., sodium hydroxide) are not "distinguishable" species, but the ionic  
217 species (i.e., sodium ion) and the buffer system containing the weak acid (i.e., acetic acid) and its  
218 conjugate base (i.e., acetate) are. Regardless of the components used in creating the buffer, the  
219 equilibrium of these species in the solution is dependent on the pH of the drug product:

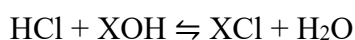


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225 Buffers are considered “exception excipients” in drug products intended for parenteral,  
226 ophthalmic, or otic use, meaning that a Q1 or Q2 difference is permitted, provided that the  
227 ANDA applicant identifies and characterizes the difference and provides information  
228 demonstrating that the difference does not affect the safety or efficacy of the proposed drug  
229 product.<sup>27</sup> In some instances, where a drug product intended for parenteral, ophthalmic, or otic  
230 use lists a pH adjuster separate from a buffer, the pH adjuster may act as part of the buffer  
231 system, but will nonetheless be treated as a pH adjuster, a non-exception excipient.

232  
233 In achieving its intended purpose (i.e., adjusting the pH), a pH adjuster may also interact with  
234 components in the formulation to form a salt. For example, a simple neutralization reaction as  
235 shown below can occur where a base inactive ingredient (XOH) is neutralized by adding  
236 hydrochloric acid (HCl), which may also be used as a pH adjuster, to form the salt of the inactive  
237 ingredient (XCl) and water:



238  
239  
240  
241 Notably, the same chemical composition can be achieved through different routes (e.g., in the  
242 prior example, the same result could also be achieved by adding XCl to H<sub>2</sub>O).<sup>28</sup>

### 243 244 245 **B. A Q1 or Q2 Difference in pH Adjuster May Be Appropriate in an ANDA in** 246 **Certain Circumstances**

247  
248 The Agency’s experience with pH adjusters, coupled with the specific role pH adjusters  
249 generally play in drug formulations, support the conclusion that in certain circumstances it may  
250 be appropriate for FDA to consider a waiver to permit a Q1 or Q2 difference in a pH adjuster(s)  
251 in a generic drug product intended for parenteral, ophthalmic, or otic use.

252  
253 The Agency has approved many new drug applications for RLDs intended for parenteral,  
254 ophthalmic, or otic use where the applicant specifies the amount of pH adjuster used as q.s.  
255 Where an RLD is approved with a q.s. amount of pH adjuster, it is possible for a relative amount  
256 of pH adjuster added to a specific batch of the RLD to differ from batch to batch, based on the  
257 amount of pH adjuster needed to achieve the specified pH or pH range for a particular RLD  
258 batch. In approving an application under these circumstances, the Agency has determined as a  
259 scientific matter that the acceptability of the finished product (containing the as-needed amount  
260 of the pH adjuster) is assured by controlling the drug product’s physicochemical characteristics  
261 (e.g., pH, osmolality, viscosity). In some instances, the use and amount of pH adjuster between  
262 batches of the RLD may exceed 5% while not changing the drug product’s final attributes in an  
263 unacceptable manner (e.g., changing the pH or physicochemical characteristics that may be  
264 critical to the drug product’s performance) or affecting the safety or efficacy of the RLD. Thus,

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<sup>27</sup> See 21 CFR 314.94(a)(9)(iii), (iv); see also 21 CFR 314.127(a)(8)(ii)(B), (C).

<sup>28</sup> An ingredient that solely acts to convert an active ingredient (e.g., from a base form to a salt form) during manufacturing of the drug product is not considered an inactive ingredient (because it becomes part of the active ingredient) and is therefore outside of the intended scope of this guidance, which concerns the requirements for inactive ingredients in drug products intended for parenteral, ophthalmic, or otic use.

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265 wide ranges in the amount of pH adjuster may be acceptable provided that the drug product's  
266 final attributes are adequately controlled.

267  
268 Applying these scientific principles to instances where the RLD is approved with a fixed amount  
269 of pH adjuster, FDA has also concluded that there may be circumstances where an ANDA  
270 applicant can establish that a greater than 5% difference in the amount of pH adjuster in an  
271 ANDA product compared to the RLD would not change the proposed drug product's final  
272 attributes in an unacceptable manner (e.g., changing the pH or physicochemical characteristics  
273 that may be critical to the drug product's performance) or cause the drug product to not meet the  
274 statutory standards for approval of an ANDA.<sup>29</sup> For example, an ANDA applicant may choose to  
275 submit, and the Agency will review and consider, a waiver request to use an amount of a pH  
276 adjuster that is more than 5% higher than the amount contained in the RLD. In such a  
277 circumstance, a waiver request under § 314.99(b) should include supportive information to  
278 scientifically justify the difference in pH adjuster. For instance, with respect to the safety of a  
279 proposed quantitative difference in pH adjuster, an applicant may include supportive information  
280 from the Inactive Ingredients Database (IID),<sup>30</sup> and/or other information as needed, as part of its  
281 scientific justification for the difference in pH adjuster.

282  
283 It is also notable that RLD application holders for drug products intended for parenteral,  
284 ophthalmic, or otic use may elect to include in their composition tables one or multiple pH  
285 adjusters, which are used on an as-needed basis. Thus, although included in the composition  
286 table, a pH adjuster(s) may, or may not, be present in a given RLD batch. For example, an RLD  
287 application holder may indicate in a composition table that pH adjuster A "and/or" B may be  
288 used q.s. Under this scenario, only pH adjuster A, only pH adjuster B, both pH adjusters, or  
289 neither pH adjuster may be included in any given RLD batch.

290  
291 The scientific principle underlying this practice for an RLD may also support the conclusion that  
292 the omission or addition of a pH adjuster in an ANDA product referencing such an RLD, like the  
293 omission or addition of an exception excipient enumerated in § 314.94(a)(9)(iii) and (iv), may,  
294 in certain circumstances, not change the ANDA's final attributes in an unacceptable manner  
295 (e.g., change the pH or physicochemical characteristics that may be critical to the drug product's  
296 performance). In such case, such a change might be permissible in an ANDA if a waiver is  
297 requested and granted and as long as the drug product meets the standards for approval of an  
298 ANDA.<sup>31</sup> For example, an ANDA applicant may choose to submit, and the Agency will review  
299 and consider, a waiver request to use a pH adjuster that has been previously used in an approved  
300 drug product for the same route of administration<sup>32</sup> but that is not used in the RLD. In such a  
301 circumstance, a waiver request under § 314.99(b) should include supportive information to  
302 scientifically justify the difference in pH adjuster. For instance, with respect to the safety of a  
303 proposed qualitative difference in pH adjuster, an applicant may include supportive information

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<sup>29</sup> See *infra* Part IV (providing recommendations on the type of information that can be submitted to support a waiver request, including information showing that the Q1 or Q2 difference does not affect safety or efficacy).

<sup>30</sup> See *id*; see also FDA's draft guidance for industry *Using the Inactive Ingredient Database* (July 2019). When final, this guidance will represent FDA's current thinking on this topic.

<sup>31</sup> See *infra* Part IV (discussing the type of information that can be submitted to support a waiver request, including information showing that the Q1 or Q2 difference does not affect safety or efficacy).

<sup>32</sup> See, e.g., 21 CFR 314.127(a)(8)(ii)(A)(2), (3), (4).

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304 from the IID, and/or other information as needed, as part of its scientific justification for the  
305 difference in pH adjuster.

306  
307 It is important to note, however, that determining the acceptability of any particular difference in  
308 pH adjuster is a fact-specific inquiry based on the circumstances of a particular application.  
309 There are differences that will likely not be acceptable for an ANDA and thus FDA would deny  
310 a waiver request submitted for such differences. For instance, FDA will deny a waiver request if  
311 the difference in pH adjuster: forms a different form of the active ingredient than the RLD in the  
312 final product; or uses or forms a novel inactive ingredient in the final product that has not been  
313 used in an FDA-approved drug product, the safety of which cannot be established without  
314 clinical testing. These types of pH adjuster differences are not appropriate for an ANDA. In  
315 addition, FDA may deny a waiver request if the difference in pH adjuster impacts the physical or  
316 chemical properties critical to the performance of the product or where those property changes  
317 raise potential safety concerns. For example, there may be potential safety concerns where an  
318 ANDA uses a different pH adjuster to the RLD, and that difference gives rise to either a new  
319 counter-ion species not present in the RLD or a different concentration of the counter-ion species  
320 than the RLD. Additionally, a change in counter-ion concentration or species may impact the  
321 physicochemical properties of complex formulations, which may alter the performance of the  
322 drug product in ways that may not be appropriate for approval in an ANDA (e.g., final pH is  
323 different from the pH listed by the RLD).

324  
325

### **IV. INFORMATION FDA MAY CONSIDER WHEN EVALUATING A REQUEST FOR WAIVER FOR A pH ADJUSTER IN AN ANDA**

328

329 As described above, in certain cases, a proposed Q1 or Q2 difference in a pH adjuster(s) in a  
330 generic drug product intended for parenteral, ophthalmic, or otic use may be acceptable in an  
331 ANDA. The general principles discussed in Section III above regarding the role pH adjusters  
332 play may support a waiver of the Q1 requirement when an ANDA applicant seeks to omit a pH  
333 adjuster, add a pH adjuster, or use a different pH adjuster compared to the RLD; and/or a waiver  
334 of the Q2 requirement when the RLD has specified a fixed quantity for a pH adjuster and an  
335 ANDA applicant seeks to use a different quantity. If an ANDA applicant believes it is  
336 appropriate to seek approval for a product with such a difference from its RLD, the ANDA  
337 applicant should submit a waiver request under § 314.99(b) to support the proposed difference.<sup>33</sup>  
338 However, as noted above, there may be instances where certain differences in pH adjuster may  
339 not be appropriate in an ANDA. To assist FDA in evaluating whether a waiver request for a pH  
340 adjuster in an ANDA intended for parenteral, ophthalmic, or otic use is appropriate, FDA  
341 recommends that applicants provide certain information, described below.

342

343 To support a waiver request, FDA recommends that applicants submit information about a  
344 proposed product's physicochemical characterization. Physicochemical characterization

---

<sup>33</sup> Where an RLD denotes the pH adjuster quantity used as q.s., the Agency has determined that the RLD is safe and effective despite the fact that the amount of pH adjuster used may vary, as needed, from batch to batch. Under FDA's current practice, an ANDA that relies on such an RLD can propose to use a q.s. or a fixed amount of the same pH adjuster, which FDA will generally consider to be Q2 same with respect to the pH adjuster, such that a waiver request with respect to that pH adjuster would not be necessary.

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345 information might be included in an ANDA generally to identify essential physical and chemical  
346 properties of a product that may be critical to its performance. Physicochemical characterization  
347 information may also be submitted in support of a § 314.99(b) waiver request. Scientific  
348 advances have enhanced the accuracy and sensitivity of physicochemical characterization, and  
349 such characterization may be useful in evaluating the effect, if any, of a difference in pH adjuster  
350 on the performance of a proposed generic drug product compared to its RLD.

351  
352 For example, as discussed above, comparative pH can be used to support similar hydronium  
353 concentrations between the RLD and generic drug product, which helps to ensure a similar  
354 physicochemical environment including any protonation and/or deprotonation of other  
355 ingredients in the formulation. In addition, comparative buffer capacity can be used to support  
356 similar capacities to resist changes in pH between the RLD and generic drug product, which  
357 helps to ensure that the generic drug product has a similar physicochemical environment as the  
358 RLD, and that drug product stability for the proposed generic drug product is not affected.  
359 Comparative osmolality can be used to support similar total solute concentrations between the  
360 RLD and generic drug product, which helps to ensure the safety and stability of the drug product.  
361 Further, for some complex formulations, comparative viscosity<sup>34</sup> and electrophoretic mobility  
362 can be used to support similar concentrations of charged species between the RLD and generic  
363 drug product, which helps to ensure drug product quality. Similarly, in vivo or in vitro studies  
364 showing comparable active ingredient release rates between the RLD and generic drug product  
365 can be used to support a waiver concluding that differences in type or amounts of pH adjuster  
366 between the RLD and generic drug product will not preclude approval of the proposed product in  
367 an ANDA.

368  
369 In addition to information regarding physicochemical characterization, other information  
370 regarding the safety of a proposed difference in pH adjuster may be relevant to assess whether a  
371 waiver for a pH adjuster difference in an ANDA would be appropriate. For example, if the  
372 generic drug product proposes to contain a different pH adjuster or a higher amount of pH  
373 adjuster than that used in the RLD, then the Agency recommends that the ANDA applicant, at a  
374 minimum, include in support of its waiver request information showing that (1) the proposed pH  
375 adjuster has been used in drug products previously approved by FDA for the same route of  
376 administration, and (2) the amount of pH adjuster used can be considered safe based on the  
377 amount of that pH adjuster in previously approved drug products for the same route of  
378 administration.

379  
380 In summary, the Agency recommends applicants consider submitting the following types of  
381 information for the proposed generic drug product and its RLD to assist FDA in evaluating a  
382 waiver request for a difference in pH adjuster in a proposed ANDA intended for parenteral,  
383 ophthalmic, or otic use (more or less information may be necessary depending on the proposed  
384 difference):<sup>35</sup>

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<sup>34</sup> Because viscosity may be an important attribute that governs availability of the drug at the site of action, comparable viscosity can support a showing that differences in pH adjuster between the generic drug product and its RLD should not affect BE.

<sup>35</sup> For example, in general, the information that would be recommended to support a waiver request for a solution may be less extensive than the information recommended to support a waiver request for a suspension, gel, or emulsion.

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- 385
- 386       • Comparative pH, buffer capacity, or both (where applicable).
- 387
- 388       • Comparative osmolality.
- 389
- 390       • Comparative viscosity.
- 391
- 392       • Comparative electrophoretic mobility.
- 393
- 394       • Comparative concentration of the pH adjuster ingredient being reacted with to form the
- 395       new salt or free base/acid species,<sup>36</sup> including data or information that demonstrates that
- 396       the new salt or free base/acid species does not affect the safety of the proposed drug
- 397       product, for example, reference to the IID.
- 398
- 399       • Other comparative physicochemical data (e.g., which may support the use of pH adjusters
- 400       in concentrations greater than  $\pm 5\%$  of the amount used in the RLD).
- 401
- 402       • Data or information that demonstrates that the difference in the amount of pH adjuster,
- 403       the number or identity of pH adjusters, or both (as applicable) between the proposed drug
- 404       product and its RLD does not affect the safety of the proposed drug product, including,
- 405       for example, reference to the IID.
- 406
- 407       • Data or information that demonstrates that the difference in the amount of pH adjuster or
- 408       the number or identity of pH adjusters between the proposed drug product and its RLD
- 409       does not affect bioequivalence (BE). For example, pharmacokinetic data from in vivo BE
- 410       studies for non-solution products or in vitro release testing data from in vitro BE studies.
- 411
- 412

### **V. TIMING AND PROCESS FOR SUBMISSION AND FDA CONSIDERATION OF A 314.99(b) WAIVER REQUEST**

#### **A. Process and Format for Requesting a Waiver**

413

414

415

416

417

418 FDA recommends that an ANDA applicant developing a proposed drug product intended for

419 parenteral, ophthalmic, or otic use submit a controlled correspondence<sup>37</sup> requesting an evaluation

420 of the proposed formulation and the RLD. If the response to the controlled correspondence

421 indicates that the proposed formulation does not meet the inactive ingredient requirements

422 applicable to the product, and the ANDA applicant believes that this failure to meet such

423 requirements is due to a difference in pH adjuster(s), the ANDA applicant may consider

424 submitting a § 314.99(b) waiver request to support the pH adjuster difference in its ANDA

425 submission.

426

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<sup>36</sup> The formation of a new salt or free base/acid species discussed here does not include a new salt or free base/acid species of the active ingredient(s).

<sup>37</sup> See FDA's guidance for industry *Controlled Correspondence Related to Generic Drug Development* (December 2020).

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427 If an ANDA applicant chooses to submit its ANDA without utilizing the controlled  
428 correspondence process and believes its formulation may not meet the inactive ingredient  
429 requirements in § 314.94(a)(9)(iii)-(iv) with respect to one or more pH adjusters, FDA  
430 recommends such ANDA applicant submit a § 314.99(b) waiver request with the ANDA.  
431

432 In accordance with § 314.99(b) (by reference to 21 CFR 314.90(a)), the waiver request and its  
433 supporting documentation must be submitted in an ANDA, or in an amendment or supplement to  
434 an ANDA (hereinafter referred to as an “ANDA submission”) where appropriate (e.g., an  
435 amendment or supplement seeking to change the drug product formulation). The Agency will  
436 refuse to receive an ANDA for a proposed product intended for parenteral, ophthalmic, or otic  
437 use that contains a Q1 or Q2 difference in pH adjuster compared to its RLD but does not include  
438 a waiver request.<sup>38</sup> In addition, FDA does not consider an inquiry about a waiver request via  
439 controlled correspondence or pre-ANDA meeting request to constitute a waiver request. FDA  
440 will not consider a waiver request unless the request and the accompanying documentation are  
441 included in an ANDA submission, consistent with the requirements of § 314.90 and § 314.99(b).  
442

443 FDA recommends that an ANDA submission containing a waiver request prominently identify in  
444 the cover letter to the submission in Module 1 of the Common Technical Document that a waiver  
445 request is included.<sup>39</sup> FDA recommends that applicants submit the waiver request in the module,  
446 section, and subsection of the ANDA submission that would otherwise address the regulatory  
447 requirement for which the waiver request is being submitted.<sup>40</sup> For additional recommendations  
448 about the information that should be ordinarily submitted in the applicable modules, sections,  
449 and subsection of ANDA submissions, please consult FDA’s guidance for industry *ANDA*  
450 *Submissions—Content and Format* (June 2019).  
451

### **B. Content of a Waiver Request**

452  
453  
454 As noted above, a waiver request must be submitted (with supporting documentation) in an  
455 ANDA submission.<sup>41</sup> Under the applicable regulations, a waiver request must contain at least  
456 one of the following:  
457

- 458 (1) An explanation why the applicant’s compliance with the requirement is unnecessary or  
459 cannot be achieved;
- 460 (2) A description of an alternative submission that satisfies the purpose of the requirement; or  
461 (3) Other information justifying a waiver.<sup>42</sup>  
462  
463  
464

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<sup>38</sup> See 21 CFR 314.94(a)(9)(iii), (iv); see also FDA’s guidance for industry *ANDA Submissions—Refuse-to-Receive Standards* (December 2016) at Part V.A.2. (discussing product quality deficiencies for changes to non-exception inactive ingredients in drug products intended for parenteral, ophthalmic, or otic use).

<sup>39</sup> See FDA’s revised guidance for industry *Providing Regulatory Submissions in Electronic Format—Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (January 2019) for more information on the contents of Module 1 of the Common Technical Document.

<sup>40</sup> *Id.*

<sup>41</sup> See 21 CFR 314.99(b) (referencing 314.90(a)).

<sup>42</sup> See 314.90(a).

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465 To ensure the Agency is clear on which information in the ANDA submission is intended to  
466 support the waiver request, FDA recommends applicants include the following information in  
467 the ANDA submission cover letter in the section that specifically discusses the waiver request:  
468

- 469 • Relevant RLD(s), as applicable, including application number, proprietary (brand) name,  
470 manufacturer, active ingredient, dosage form, and strength(s);  
471
- 472 • Statement describing the Q1 or Q2 difference in pH adjuster for which the applicant is  
473 requesting waiver of the applicable regulatory requirement;  
474
- 475 • Summary of the type of information submitted to support the waiver request; and  
476
- 477 • Identification of the module, section, and subsection of the ANDA submission that  
478 contains the waiver request and the information submitted to support the waiver request.  
479

### **C. Waiver Request Outcome**

480

481 The Agency may grant a waiver request if it finds one of the following:  
482

483

484 (1) The applicant's compliance with the requirement is unnecessary for the Agency to  
485 evaluate the ANDA or compliance cannot be achieved;

486

487 (2) The applicant's alternative submission satisfies the requirement; or  
488

488

489 (3) The applicant's submission otherwise justifies a waiver.<sup>43</sup>  
490

490

491 The acceptability of a waiver request will be determined during the scientific review of an  
492 ANDA. FDA will inform applicants of the Agency's decision regarding a waiver request when  
493 FDA acts on the ANDA containing the waiver request.<sup>44</sup>  
494

494

### **D. Effect on Eligibility to Use Certain Approaches to Show Bioequivalence**

495

496

497 FDA recognizes that where an ANDA applicant wishes to seek a waiver of the inactive  
498 ingredient requirements at § 314.94(a)(9)(iii) or (iv) for a Q1 or Q2 difference in pH adjuster  
499 compared to its RLD, that applicant might also seek to utilize an in vitro approach to  
500 demonstrate BE. However, if FDA grants a waiver for an ANDA's Q1 or Q2 difference in pH  
501 adjuster, then that ANDA product necessarily does not contain the same inactive ingredients in  
502 the same concentration as its RLD. Thus, such an ANDA product would not be eligible under 21  
503 CFR 320.22(b)(1) for a waiver of evidence of in vivo BE. Under 21 CFR 320.24(b)(6), however,  
504 an approach "deemed adequate by FDA to ... establish bioequivalence" may be utilized to  
505 establish BE of a drug product where scientifically appropriate. FDA encourages an applicant  
506 who submits a waiver of the inactive ingredients requirement at § 314.94(a)(9)(iii) or (iv) for a

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<sup>43</sup> See 21 CFR 314.90(a).

<sup>44</sup> See GDUFA Reauthorization Performance Goals and Program Enhancements, Fiscal Years 2018-2022, available at <https://www.fda.gov/media/101052/download> ("Act on an application – means FDA will either issue a complete response letter, an approval, a tentative approval, or a refuse-to-accept action.").



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507 difference in pH adjuster and who also seeks to use an in vitro approach to demonstrate BE, to  
508 contact the Agency to discuss the particular approach to establish BE for that particular drug  
509 product.

510  
511 Similarly, FDA's product specific guidances (PSG) may recommend that an ANDA product  
512 contain the same inactive ingredients in the same concentration as its RLD to use a particular  
513 approach recommended in the PSG to demonstrate BE. Recommendations in PSGs are not  
514 binding, and applicants may use an alternative approach if it satisfies the requirements of the  
515 applicable statutes and regulations. The scientific principles described in this guidance that  
516 provide support for a waiver of the inactive ingredient requirements under § 314.94(a)(9)(iii) and  
517 (iv) for a difference in pH adjuster may, in some cases, also provide support for an applicant's  
518 scientific justification for use of a particular BE approach. As noted above, FDA encourages an  
519 applicant, who submits a waiver of the inactive ingredients requirement at § 314.94(a)(9)(iii) or  
520 (iv) for a difference in pH adjuster and who also seeks to use an in vitro approach to demonstrate  
521 BE, to contact the Agency to discuss the particular approach to establish BE for that particular  
522 drug product.