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# New Clinical Investigation Exclusivity (3-Year Exclusivity) for Drug Products: Questions and Answers Guidance for Industry

## *DRAFT GUIDANCE*

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For questions regarding this draft document, contact (CDER) Susan Levine 240-402-7936.

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

**March 2026  
Procedural**

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*Draft — Not for Implementation*

# New Clinical Investigation Exclusivity (3-Year Exclusivity) for Drug Products: Questions and Answers Guidance for Industry

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

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1 **New Clinical Investigation Exclusivity (3-Year Exclusivity) for Drug**  
2 **Products: Questions and Answers**  
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6 This draft guidance, when finalized, will represent the current thinking of the Food and Drug  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

12  
13  
14 **I. INTRODUCTION**  
15

16 This guidance is intended to assist applicants requesting New Clinical Investigation exclusivity  
17 (also referred to as 3-year exclusivity) for a new drug application (NDA) or NDA supplement  
18 under sections 505(c)(3)(E)(iii)-(iv) and 505(j)(5)(F)(iii)-(iv) of the Federal Food, Drug, and  
19 Cosmetic Act (FD&C Act). The guidance discusses the statutory and regulatory criteria for  
20 eligibility for New Clinical Investigation exclusivity and provides recommendations on the  
21 content and format of requests for New Clinical Investigation exclusivity in the form of  
22 questions and answers (Q&As). FDA intends to update this draft guidance document to include  
23 additional Q&As as appropriate.  
24

25 In general, FDA’s guidance documents do not establish legally enforceable responsibilities.  
26 Instead, guidances describe the Agency’s current thinking on a topic and should be viewed only  
27 as recommendations, unless specific regulatory or statutory requirements are cited. The use of  
28 the word should in Agency guidances means that something is suggested or recommended, but  
29 not required.  
30

31  
32 **II. BACKGROUND**  
33

34 The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417)  
35 (Hatch-Waxman Amendments), which added sections 505(b)(2) and 505(j) to the FD&C Act (21  
36 U.S.C. sections 355(b)(2) and 355(j)), reflects Congress’s efforts to balance the need to “make  
37 available more low cost generic drugs by establishing a generic drug approval procedure” with  
38 new incentives for drug development in the form of exclusivities and patent term extensions.<sup>2</sup>  
39 These incentives include a 3-year period of exclusivity for drugs approved in certain NDAs or  
40 supplements to NDAs during which applications submitted pursuant to section 505(b)(2) of the  
41 FD&C Act (505(b)(2) applications) and abbreviated new drug applications submitted under

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

<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.

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42 section 505(j) of the FD&C Act (ANDAs or 505(j) applications) may not be approved for  
43 exclusivity-protected conditions of approval of such drugs.<sup>3</sup>

44  
45 An application may qualify for 3-year exclusivity if it is a 505(b) application or supplement to a  
46 505(b) application:

- 47
- 48 • for a drug, which includes an active moiety<sup>4</sup> that has been approved in another  
49 505(b) application (or, for a fixed-combination drug product where each of the  
50 active moieties were previously approved in another 505(b) application); and
  - 51 • that contains reports of new clinical investigations that are:
    - 52 i. Not bioavailability studies;
    - 53 ii. Essential to the approval of the application (or supplement); and
    - 54 iii. Conducted or sponsored by the applicant.<sup>5</sup>
- 55

56 On October 3, 1994, FDA issued a final rule,<sup>6</sup> which, in relevant part, defined terms in the  
57 exclusivity provisions of the FD&C Act and established the framework for the timing of  
58 approval for a 505(b)(2) application or ANDA impacted by New Clinical Investigation  
59 exclusivity.<sup>7</sup> As a general matter, FDA has implemented the relevant statutory and regulatory  
60 provisions within the context of application-specific decisions. Some FDA decisions have been  
61 made publicly available (e.g., in FDA citizen petition responses and documents released in  
62 litigation). FDA believes that a guidance for industry that provides answers to commonly asked  
63 questions about 3-year exclusivity would enhance transparency and help facilitate the  
64 development, approval, and timely marketing of innovator and follow-on drug products.

65  
66 Using a Q&A format, this guidance discusses each of the statutory and regulatory criteria for  
67 eligibility for 3-year exclusivity mentioned above<sup>8</sup> and clarifies the processes for applicants to  
68 request 3-year exclusivity, for FDA to make 3-year exclusivity eligibility determinations, and for  
69 providing notice of those determinations in FDA's *Approved Drug Products with Therapeutic  
70 Equivalence Evaluations* (the "Orange Book").

71  
72

### **III. QUESTIONS AND ANSWERS**

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74

#### **A. General Eligibility For 3-Year Exclusivity**

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##### **QA.1. What applications are eligible for 3-year exclusivity?**

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78

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<sup>3</sup> See sections 505(c)(3)(E)(iii) and (iv), and 505(j)(5)(F)(iii) and (iv) of the FD&C Act.

<sup>4</sup> Active moiety is defined as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance" (21 CFR 314.3(b)).

<sup>5</sup> See sections 505(c)(3)(E)(iii) and (iv), and 505(j)(5)(F)(iii) and (iv) of the FD&C Act.

<sup>6</sup> 59 FR 50338.

<sup>7</sup> 21 CFR 314.108.

<sup>8</sup> The eligibility criteria for 3-year exclusivity for antibiotic drugs subject to section 505(v) of the FD&C Act are not discussed in this draft guidance.

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79 An NDA that seeks approval of a drug product containing an active moiety that was  
80 previously approved in another 505(b) application (or, for a fixed-combination drug  
81 product where each of the active moieties were previously approved in another 505(b)  
82 application) is eligible for a 3-year period of exclusivity when that application contains  
83 reports of new clinical investigations (other than bioavailability studies) that were  
84 essential to the approval of the application and conducted or sponsored by the applicant.  
85

86 The first clause in section 505(c)(3)(E)(iii) and section 505(j)(5)(F)(iii) of the FD&C Act,  
87 often referred to as the eligibility clause, describes the applications eligible for 3-year  
88 exclusivity:

89  
90 If an application submitted under subsection (b) [of this section] for a drug,  
91 which includes an active moiety (as defined by the Secretary in section 314.3 of  
92 title 21, Code of Federal Regulations (or any successor regulations)) that has  
93 been approved in another application approved under subsection (b) [of this  
94 section], is approved after [September 24, 1984], and if such application contains  
95 reports of new clinical investigations (other than bioavailability studies) essential  
96 to the approval of the application and conducted or sponsored by the applicant. . .  
97

### **QA.2. Are supplements to approved applications eligible for 3-year exclusivity?**

98  
99

100 Sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) describe the circumstances under which  
101 FDA will recognize 3-year exclusivity for a supplement to a 505(b) application. A  
102 supplement to an approved NDA may be eligible for 3-year exclusivity if the submission  
103 contains reports of new clinical investigations (other than bioavailability studies) that  
104 were essential to the approval of the supplement and conducted or sponsored by the  
105 applicant submitting the supplement.<sup>9</sup> In such instances, the 3-year period of exclusivity  
106 is recognized only for the change(s) approved in the supplement to the NDA that is  
107 supported by the new clinical investigation(s) essential to the approval of the supplement  
108 and conducted or sponsored by the applicant submitting the supplement. It does not also  
109 provide a new 3-year period of exclusivity for previously approved conditions of  
110 approval for the drug product containing the same active moiety. In general, changes that  
111 may qualify for 3-year exclusivity (provided the statutory and regulatory requirements  
112 are satisfied) are typically submitted in an efficacy supplement.<sup>10</sup>  
113  
114

## **B. New Clinical Investigations**

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116

### **QB.1. What is a *clinical investigation* for purposes of 3-year exclusivity?**

117  
118

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<sup>9</sup> See sections 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv) of the FD&C Act.

<sup>10</sup> See the definition of *efficacy supplement* in 21 CFR § 314.3(b).

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119 FDA’s regulations implementing the Hatch-Waxman exclusivity provisions define a  
120 *clinical investigation* as “any experiment other than a bioavailability study in which a  
121 drug is administered or dispensed to, or used on, human subjects.”<sup>11,12</sup>  
122

### **QB.2. Does the drug used in the clinical investigation need to be the same as that approved for the application to qualify for 3-year exclusivity?**

123  
124  
125  
126 FDA does not require the drug used in the clinical investigation to be the same as that  
127 approved for the application to qualify for 3-year exclusivity provided that all  
128 requirements of 21 CFR § 314.108 and section 505(c)(3)(E)(iii) or (iv) of the FD&C Act  
129 are met. For example, a clinical investigation that used a similar or earlier version of the  
130 drug product in development, which contains the same active moiety or combination of  
131 active moieties as the version of the drug in the approved application, may potentially  
132 qualify the approved drug product for 3-year exclusivity. To illustrate, if a clinical  
133 investigation used a granule formulation of a drug, but the NDA at issue is seeking  
134 approval for a tablet dosage form of that drug, which could be crushed and administered  
135 similarly to the granule formulation, the clinical investigation nevertheless may qualify  
136 the tablet for 3-year exclusivity, provided the statutory and regulatory criteria are met.  
137

### **QB.3. Could a clinical investigation that only administered placebo to study participants qualify as a *clinical investigation* for 3-year exclusivity?**

138  
139  
140  
141 FDA generally does not consider an investigation that only administers placebo to study  
142 participants to meet the definition of *clinical investigation*. A clinical investigation that  
143 only administers placebo to study participants is not an “experiment other than a  
144 bioavailability study in which a drug is administered or dispensed to, or used on, human  
145 subjects” as that phrase is used in the definition of *clinical investigation* at § 314.108(a).  
146 As such, a clinical investigation that only administers placebo to study participants would  
147 not qualify for 3-year exclusivity.  
148

### **QB.4. What is a *bioavailability study*?**

149  
150  
151 A *bioavailability study* is defined in FDA regulations as “a study to determine the  
152 bioavailability or the pharmacokinetics of a drug.”<sup>13</sup> Bioavailability is defined in FDA  
153 regulations as:

154  
155 the rate and extent to which the active ingredient or active moiety is absorbed  
156 from a drug product and becomes available at the site of drug action. For drug  
157 products that are not intended to be absorbed into the bloodstream, bioavailability  
158 may be assessed by scientifically valid measurements intended to reflect the rate

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<sup>11</sup> 21 CFR 314.108(a).

<sup>12</sup> Note that “Congress intended the term ‘clinical’ to mean human studies, and intentionally excluded all animal studies, regardless of the purpose for which they are conducted.” See FDA’s preamble to its proposed regulations implementing Title I of the Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. 98-417), 54 FR 28872, 28899 (July 10, 1989) (citing Zenith Laboratories, Inc. v. Heckler, No. 85-3646 (D.N.J. May 19, 1986)).

<sup>13</sup> 21 CFR 314.108(a).

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159 and extent to which the active ingredient or active moiety becomes available at  
160 the site of drug action.<sup>14</sup>

161  
162 As described in the regulations, bioavailability may be measured by several in vivo and  
163 in vitro testing methods, such as pharmacokinetic (PK) studies.<sup>15</sup> Studies using a variety  
164 of testing methods may qualify as a bioavailability study. For example, while PK studies  
165 are preferred for measuring the bioavailability of orally administered drug products when  
166 the drug is absorbed into systemic circulation, in certain instances, PK studies are not  
167 feasible. In such instances, in vivo tests in humans in which an acute pharmacological  
168 effect of the active moiety and, when appropriate, its active metabolite(s), are measured  
169 as a function of time (i.e., a pharmacodynamic study) might be utilized for measuring  
170 bioavailability of the drug product if such effect can be measured with sufficient  
171 accuracy, sensitivity, and reproducibility.<sup>16</sup> Such pharmacodynamic studies may be  
172 considered bioavailability studies in these instances.

### 173 174 **QB.5. Could an investigation assessing both PK/bioavailability and clinical safety** 175 **and/or effectiveness qualify as a *clinical investigation* for 3-year exclusivity?**

176  
177 Yes. A study may have one or more purposes, including one or more primary purposes,<sup>17</sup>  
178 which FDA may determine by examining, among other things, its endpoints, its design,  
179 and/or its role in the evidentiary package. For example, some studies may incorporate the  
180 assessment of a safety and/or effectiveness endpoint to support approval (for the purpose  
181 of demonstrating safety and/or effectiveness of the drug) in conjunction with a PK  
182 assessment. Although the PK assessment is intended to characterize bioavailability, the  
183 Agency may find that the inclusion of the assessment of the safety and/or effectiveness  
184 endpoint in the study means that such a study meets the definition of a *clinical*  
185 *investigation* for purposes of 3-year exclusivity, notwithstanding the collection of  
186 PK/bioavailability data in the same study. However, for example, studies that FDA  
187 concludes were conducted for the sole purpose of determining PK/bioavailability and  
188 merely incorporate routine safety monitoring of adverse events or reactions (as is  
189 generally required for all studies of drugs in humans, including bioavailability studies)  
190 would generally not be considered a *clinical investigation* for purposes of 3-year  
191 exclusivity.

### 192 193 **QB.6. When is a clinical investigation considered a *new clinical investigation* for** 194 **purposes of 3-year exclusivity?**

---

<sup>14</sup> 21 CFR 314.3(b).

<sup>15</sup> 21 CFR 320.24. See also the guidance for industry *Bioavailability Studies Submitted in NDAs or INDs — General Considerations* (April 2022). 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>.

<sup>16</sup> 21 CFR 320.24(b)(3).

<sup>17</sup> See *Liquidia Techs., Inc. v. FDA*, Civ. A. No. 24-2428, 2025 WL 637413, at \*7 (D.D.C. Feb. 27, 2025) (holding that the study in question in that case was a clinical investigation (other than a bioavailability study) because its primary purpose, as shown in that case by its primary endpoint, was to evaluate safety and tolerability, notwithstanding that the study also assessed bioavailability).

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196 FDA has defined a *new clinical investigation* as a clinical investigation in which the  
197 results:

- 198 • Have not been relied on by FDA to demonstrate substantial evidence of  
199 effectiveness of a previously approved drug product for any indication or of safety  
200 for a new patient population, and
- 201 • Do not duplicate the results of another investigation that was relied on by the  
202 Agency to demonstrate the effectiveness or safety in a new patient population of a  
203 previously approved drug product<sup>18</sup>

204  
205  
206 In addition, FDA’s regulations state that “data from a clinical investigation previously  
207 submitted for use in the comprehensive evaluation of the safety of a drug product but not  
208 to support the effectiveness of the drug product would be considered new.”<sup>19</sup>

### **QB.7. What information is an applicant expected to provide to show that its NDA<sup>20</sup> contains new clinical investigations?**

209  
210  
211  
212  
213 To show that the NDA contains new clinical investigations, the applicant must include a  
214 certification that to the best of its knowledge: (1) each of the clinical investigations is an  
215 investigation in humans; (2) the results of which have not been relied on by FDA to  
216 demonstrate substantial evidence of effectiveness of a previously approved drug product  
217 for any indication or of safety for a new patient population; and (3) do not duplicate the  
218 results of another investigation that was relied on by the Agency to demonstrate the  
219 effectiveness or safety in a new patient population of a previously approved drug  
220 product<sup>21</sup> (see QE.1 on the process for requesting 3-year exclusivity). In the past,  
221 supportive information for the certification has included a statement indicating that the  
222 study results have never been previously submitted to FDA; a list of other applications  
223 for which the results of the clinical investigation may have been previously submitted but  
224 not relied on for substantial evidence of effectiveness or safety for a new patient  
225 population of a previously approved drug product; or an explanation of how the clinical  
226 investigation differs from another investigation previously relied on by the Agency for  
227 effectiveness or safety for a new patient population of a previously approved drug  
228 product. FDA will evaluate the information submitted by the applicant, and the Agency  
229 will determine whether the NDA contains “new clinical investigations” under the statute  
230 and regulations.

### **QB.8. When a study involves multiple cohorts or treatment arms, could an investigation of a cohort or treatment arm qualify as a *new clinical investigation* when the results of at least one different cohort or treatment arm were previously relied on for approval of an application?**

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<sup>18</sup> 21 CFR 314.108(a).

<sup>19</sup> *Id.*

<sup>20</sup> The term NDA also includes any supplements to the NDA. See 21 CFR 314.3(b).

<sup>21</sup> See § 314.50(j)(4)(i) and the definition of *new clinical investigation* in § 314.108(a).

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237 In certain cases, an *investigation of a cohort or treatment arm* (hereinafter cohort or  
238 treatment arm for brevity) may qualify as a new clinical investigation, and thus support  
239 the eligibility of an NDA for 3-year exclusivity (if the other statutory and regulatory  
240 requirements are met), when:

- 241 1) the cohort or treatment arm could be characterized as a clinical  
242 investigation,<sup>22</sup>
- 243 2) FDA has not previously relied on the results of that specific cohort or  
244 treatment arm to demonstrate substantial evidence of effectiveness of a  
245 previously approved drug product for any indication or of safety for a new  
246 patient population, and
- 247 3) the results do not duplicate those of another investigation that was relied  
248 on by the Agency to demonstrate the effectiveness or safety in a new  
249 patient population of a previously approved drug product.<sup>23</sup>

251 Thus, a cohort or treatment arm may qualify as a *new clinical investigation* under certain  
252 circumstances even if FDA has previously relied on the results of a different cohort or  
253 treatment arm of the study for approval of any previously approved application (or  
254 supplement to an application). To conclude otherwise would elevate form over  
255 substance, placing administrative considerations (e.g., whether a sponsor submitted a  
256 master protocol<sup>24</sup> or a new protocol with a new alphanumeric identifier) above  
257 substantive innovations (e.g., whether a sponsor developed a drug for distinct new patient  
258 populations in different cohorts of a study or developed different drug products in  
259 different treatment arms of a study).

261 FDA applies a multifactorial approach to determine, on a case-by-case basis, whether a  
262 cohort or treatment arm constitutes a distinct new clinical investigation. Important factors  
263 in FDA’s analysis include, for example: whether there is an acceptable scientific or  
264 medical reason for the separate cohort or treatment arm; whether the separate cohort or  
265 treatment arm evaluates different patient populations and/or different drug products; and  
266 whether the separate cohort or treatment arm was prespecified<sup>25</sup> in the protocol.

268 FDA’s approach is consistent with the regulatory framework for 3-year exclusivity.<sup>26</sup>  
269 Through this approach, FDA encourages efficiencies in clinical trial design by using, for  
270

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<sup>22</sup> See 21 CFR 314.108(a) (defining clinical investigation as “any experiment other than a bioavailability study in which a drug is administered or dispensed to, or used on, human subjects”).

<sup>23</sup> See *id.*

<sup>24</sup> For more information about master protocols, see, e.g., guidance for industry *Master Protocols: Efficient Clinical Trial Design Strategies to Expedite Development of Oncology Drugs and Biologics* (Mar. 2022).

<sup>25</sup> With respect to a cohort or treatment arm, prespecification means that the cohort or treatment arm is described in the protocol before patients are enrolled in the cohort or treatment arm. The main goal of prespecification is to enhance the reliability and validity of research by reducing bias and preventing post hoc alterations to the study design or analysis methods.

<sup>26</sup> Similar considerations underpin the language in the “new clinical investigation” definition that states: “For purposes of this section, data from a clinical investigation previously submitted for use in the comprehensive evaluation of the safety of a drug product but not to support the effectiveness of the drug product would be considered new.” 21 CFR 314.108. As further explained in the preamble to the proposed rule, “[t]he agency does not

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271 example, a single protocol to evaluate multiple patient populations, to pave the way for  
272 faster and more efficient development of new medical products that reach new  
273 populations. This approach furthers FDA’s mission to approve safe and effective drugs  
274 and, when appropriate, rewards innovations through exclusivity, without penalizing  
275 sponsors for efficient and thoughtful clinical trial design. FDA’s approach incentivizes  
276 sponsors to submit results from distinct cohorts or treatment arms as soon as they are  
277 available, resulting in approval of corresponding information in drug labeling more  
278 quickly. An alternative approach whereby FDA could recognize only one period of 3-  
279 year exclusivity for multiple distinct cohorts could incentivize sponsors to wait to submit  
280 all the results from the distinct cohorts or treatment arms together to obtain a broader  
281 scope of exclusivity that could result in delayed approval of corresponding information in  
282 drug labeling. FDA’s approach also allows for exclusivity-protected information to be  
283 carved out of the labeling while making available non-protected information in the  
284 labeling.

285  
286 We recommend that the applicant submit a justification in its NDA explaining why the  
287 cohort or treatment arm should be considered a *new clinical investigation*. FDA intends  
288 to make such determinations on a case-by-case basis.

### **C. Essential to Approval**

#### **QC.1. When is an investigation *essential to approval*?**

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292  
293 *Essential to approval* means that “with regard to an investigation . . . there are no other  
294 data available that could support approval of the NDA.”<sup>27</sup> The assessment of whether a  
295 clinical investigation is essential to approval is made at or after the time of approval,  
296 based on information available at the time of approval.<sup>28</sup>

297  
298  
299  
300 To meet this standard, the clinical investigation must be “vital” to the application and  
301 there must not be any published studies (other than the applicant’s) or other information  
302 available to FDA that would allow the Agency to approve the proposed drug product for  
303 the proposed conditions of use or the change to the already approved drug product.<sup>29</sup> In  
304 other words, without the new clinical investigation, FDA would not have sufficient  
305 information to conclude that the drug product or change to the approved drug product for  
306 which the applicant is seeking approval is safe and effective. FDA does not consider an  
307 investigation to be essential to approval simply because the applicant conducted and  
308 submitted the investigation in its application or supplement for Agency review.<sup>30</sup> If other  
309 information is available to the Agency that would allow it to conclude that the proposed

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believe Congress intended to preclude use of data from a previously conducted study if such data provide *important new information in support of the applicant’s proposed change* to its drug product.” 54 FR 28872, 28899 (July 10, 1989) (emphasis added).

<sup>27</sup> 21 CFR 314.108(a).

<sup>28</sup> See 59 FR 50338 at 50359.

<sup>29</sup> *Id.* at 50357.

<sup>30</sup> *Id.* In the preamble to the proposed rule, FDA stated, “[r]ather, the studies must be truly ‘essential,’ rather than simply supportive, to qualify the application for exclusivity.” 54 FR at 28900.

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310 drug product for the proposed conditions of use or the change to the already approved  
311 drug product is safe and effective, and a clinical investigation provides data that merely  
312 supplements that information, then that clinical investigation would not be considered  
313 essential to approval.<sup>31</sup>

### **QC.2. What information must an applicant provide to show that a clinical investigation is essential to approval of the NDA or supplement?**

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317  
318 If an applicant believes its NDA is eligible for 3-year exclusivity, the applicant must  
319 submit the following information with the NDA prior to approval to support its assertion  
320 that a clinical investigation is *essential to approval*:

- 321  
322 1. A list of all published studies or publicly available reports of clinical  
323 investigations known to the applicant through a literature search that are  
324 relevant to the conditions for which the applicant is seeking approval;<sup>32</sup>
- 325 2. A certification that: (1) the applicant has thoroughly searched the scientific  
326 literature, and (2) to the best of the applicant's knowledge, the list is complete  
327 and accurate, and (3) in the applicant's opinion, such published studies or  
328 publicly available reports do not provide a sufficient basis for the approval of  
329 the conditions for which the applicant is seeking approval without reference to  
330 the new clinical investigation(s) in the NDA;<sup>33</sup> and
- 331 3. An explanation as to why the studies or reports identified from the literature  
332 search are insufficient.<sup>34</sup>

333  
334 See QE.1 on the process for requesting 3-year exclusivity for more information.  
335  
336

## **D. Conducted or Sponsored by the Applicant**

### **QD.1. When is an investigation conducted or sponsored by the applicant?**

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338  
339  
340  
341 An investigation is *conducted or sponsored by the applicant* if “before or during the  
342 investigation, the applicant was named in Form FDA-1571 filed with FDA as the sponsor  
343 of the investigational new drug [IND] application under which the investigation was  
344 conducted, or the applicant or the applicant’s predecessor in interest, provided substantial  
345 support for the investigation.”<sup>35</sup> A predecessor in interest is an entity, e.g., a corporation,  
346 that the applicant has taken over, merged with, or purchased, or from which the applicant  
347 has purchased all rights to the drug.<sup>36</sup> QD.2 addresses how an applicant must show that it  
348 conducted or sponsored a new clinical investigation.  
349

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<sup>31</sup> See 54 FR 28872 at 28900.

<sup>32</sup> 21 CFR 314.50(j)(4)(ii).

<sup>33</sup> *Id.*

<sup>34</sup> *Id.*

<sup>35</sup> 21 CFR 314.108(a).

<sup>36</sup> *Id.*

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350 In certain circumstances, an applicant can qualify as having “conducted or sponsored” an  
351 investigation if the applicant acquires exclusive rights to that study.<sup>37</sup> FDA’s regulation  
352 further clarifies that the “[p]urchase of nonexclusive rights to a clinical investigation after  
353 it is completed is not sufficient to satisfy this definition.”<sup>38</sup>

### **QD.2. What information is an applicant expected to provide to show that it has conducted or sponsored a new clinical investigation?**

358 If the NDA applicant or its predecessor in interest is identified as the IND sponsor on  
359 Form FDA 1571, the applicant must provide the IND number under which the new  
360 clinical investigation that is essential to the approval of its NDA was conducted.<sup>39</sup>

362 Alternatively, the applicant must provide information sufficient to show that it otherwise  
363 meets the criteria for having “conducted or sponsored” the investigation under FDA’s  
364 regulations. Specifically, the applicant must provide a certification stating that the  
365 applicant or its predecessor in interest provided substantial support for the clinical  
366 investigation(s) that is essential to the approval of its NDA and information supporting  
367 the certification.<sup>40</sup> This includes situations where the relevant clinical investigation was  
368 not conducted under an IND.<sup>41</sup>

369 The NDA applicant may show substantial support by providing either:

- 371 1. A certified statement from a certified public accountant that the applicant or  
372 its predecessor in interest provided 50 percent or more of the cost of  
373 conducting the study;<sup>42</sup> or
- 374 2. An explanation of why FDA should consider the applicant to have conducted  
375 or sponsored the study if neither the applicant nor its predecessor in interest  
376 provided at least 50 percent of the financial contribution to the study or  
377 sponsored the investigational new drug.<sup>43</sup>

378 To show that an entity (e.g., a corporation) is a predecessor in interest to the NDA  
379 applicant, the applicant should provide documentation showing that it has either (i) taken  
380 over, merged with, or purchased the entity, or (ii) purchased all rights to the drug from  
381 the entity.

382 As noted in QD.1, a demonstration of “conducted or sponsored” for purposes of  
383 eligibility for 3-year exclusivity is not satisfied by the purchase of nonexclusive rights to  
384

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<sup>37</sup> See 59 FR 50338 at 50358. The FD&C Act and regulations refer to “clinical investigations,” whereas the preamble to the regulations refers to “studies.” The terms “investigation” and “study” are used interchangeably throughout this draft guidance.

<sup>38</sup> 21 CFR 314.108(a).

<sup>39</sup> 21 CFR 314.50(j)(4)(iii).

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

<sup>41</sup> For example, where the clinical investigation was conducted in a foreign jurisdiction under the rules of that jurisdiction.

<sup>42</sup> See 21 CFR 314.50(j)(4)(iii). See also the definition of *conducted or sponsored by the applicant* in § 314.108(a).

<sup>43</sup> *Id.*

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387 a clinical investigation after it is completed.<sup>44</sup> To show that the “conducted or  
388 sponsored” requirement is met based on the acquisition of exclusive rights to a study, the  
389 NDA applicant should provide a certified statement that the applicant acquired such  
390 exclusive rights, along with any relevant supportive documentation. FDA will look at the  
391 totality of the information before the Agency to determine whether an applicant has  
392 acquired exclusive rights to a study.

393  
394 The applicant should submit this documentation with their claim for 3-year exclusivity  
395 (see section V.) through the electronic submissions gateway.<sup>45</sup> We recommend this  
396 submission be prominently identified, e.g., “**314.50(j) Exclusivity Claim – Conducted  
397 or Sponsored**”.

398  
399 See QE.1 on the process for requesting 3-year exclusivity for more information.  
400

### **E. Process for Requesting 3-Year Exclusivity**

#### **QE.1. How does an NDA applicant request 3-year exclusivity?**

401  
402  
403  
404 An NDA applicant that believes its drug product is eligible for 3-year exclusivity upon  
405 approval must submit the following information to FDA, in accordance with § 314.50(j),  
406 prior to approval:  
407

- 408 • A statement that the applicant is claiming exclusivity;
- 409 • A reference to the appropriate paragraph under § 314.108 that supports its claim;  
410 and
- 411 • Information to show that the NDA contains “new clinical investigations” (other  
412 than bioavailability studies) (see section II) that are “essential to approval of the  
413 NDA or supplement” (see section III) and “were conducted or sponsored by the  
414 applicant” (see section IV).  
415  
416

417  
418 The applicant should submit a claim for 3-year exclusivity through the electronic  
419 submissions gateway<sup>46</sup> and identify it prominently, for example as “**314.50(j) Exclusivity  
420 Claim.**” If a claim for 3-year exclusivity includes a justification for satisfying the  
421 conducted or sponsored criterion other than being the IND sponsor named on the form  
422 FDA 1571, we recommend that it should further be identified, such as “**314.50(j)  
423 Exclusivity Claim – Conducted or Sponsored.**” The request for 3-year exclusivity  
424 should be placed in the Module 1 folder of the NDA submission at subfolder 1.3.5.3. In  
425 the Appendix for this guidance, FDA has included some representative language that may  
426 be helpful to assist an applicant with their 3-year exclusivity request.  
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<sup>44</sup> *Id.*

<sup>45</sup> The electronic submissions gateway is available at [Electronic Submissions Gateway Next Generation \(ESG NextGen\) | FDA](#). Questions related to electronic submissions should be emailed to the CDER Electronic Submission (ESUB) Team at [esub@fda.hhs.gov](mailto:esub@fda.hhs.gov).

<sup>46</sup> See *supra* note 45.

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### **F. Exclusivity Determination by FDA**

#### **QF.1. What is FDA’s process for making 3-year exclusivity eligibility determinations?**

When an application is approved under section 505(c) of the FD&C Act, the relevant review division in the Office of New Drugs provides the Office of Generic Drugs (OGD) with a summary of facts about the application or supplement (“Exclusivity Summary”), which assists the Office of Generic Drug Policy (OGDP) in its determination of whether the application or supplement meets the statutory and regulatory criteria for eligibility for 3-year exclusivity. OGDP, which administers the Orange Book, reviews the Exclusivity Summary, the administrative record, and other relevant information and may consult the CDER Exclusivity Board,<sup>47</sup> when appropriate, for advice regarding a pending exclusivity determination. If OGDP determines that the application or supplement meets the statutory and regulatory criteria for eligibility for 3-year exclusivity, the relevant 3-year exclusivity information, including the exclusivity code and exclusivity expiration date, will be reflected in an upcoming Orange Book update.<sup>48</sup>

#### **QF.2. What is an exclusivity code and how does it relate to 3-year exclusivity?**

The exclusivity code in the Orange Book provides notice of an application’s exclusivity. Three-year exclusivity is described in the Orange Book with a letter (and sometimes numeric) code that may also be followed by a short description. The exclusivity codes are general shorthand descriptions and do not necessarily identify, with specificity, the actual scope of exclusivity.<sup>49</sup>

#### **QF.3. When are 3-year exclusivity codes assigned and added to the Orange Book?**

OGDP will assign an exclusivity code(s) to the drug product and list the code(s) in the Orange Book when FDA determines that an approved application meets the criteria for 3-year exclusivity. Updates to exclusivity-related information in the Orange Book generally occur once every two weeks. The Patents and Exclusivity Information Addendum to the Orange Book provides a complete list of and definitions for the current exclusivity codes.

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<sup>47</sup> For more information about the CDER Exclusivity Board, please see

<https://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm323412.htm>.

<sup>48</sup> Please note that if additional information or further analysis is needed to determine whether an NDA or supplemental NDA is eligible for 3-year exclusivity, then there may be a delay in the publication of an application’s exclusivity code. The absence of an exclusivity code in the Orange Book for an NDA or supplemental NDA does not necessarily mean that an exclusivity determination has been made for that application. See guidance for industry, *Orange Book Questions and Answers* (July 2022) for more information on when Orange Book updates are made.

<sup>49</sup> For example, see letter from J. Woodcock to G. Veron (Docket No. FDA-2010-P-0614), at 22-23 (May 25, 2011) (while the exclusivity code in the Orange Book described “gout flares,” the clinical trial essential to the approval of Colcrys (colchicine) 0.6 mg tablets was for the treatment of acute gout flares, not prophylaxis of gout flares, and therefore the only exclusivity-protected indication was for the treatment of acute gout flares).

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**APPENDIX: NEW CLINICAL INVESTIGATION EXCLUSIVITY REQUEST  
REPRESENTATIVE LANGUAGE**

Requests for New Clinical Investigation exclusivity (also referred to as 3-year exclusivity) should be included in the Module 1 folder of the NDA submission at subfolder 1.3.5.3 and prominently identified as “**314.50(j) Exclusivity Claim.**” Representative language for requesting 3-year exclusivity may include the following:

Exclusivity Request - New Clinical Investigation Exclusivity

[Applicant] requests 3 years of exclusivity under sections [505(c)(3)(E)(iii) and 505(j)(5)(F)(iii) or 505(c)(3)(E)(iv) and 505(j)(5)(F)(iv)] of the FD&C Act and [§ 314.108(b)(4) or § 314.108(b)(5)] and makes the following assertions pursuant to § 314.50(j)(4):

1. New Clinical Investigations: To the best of [Applicant’s] knowledge, the following clinical investigation(s) included in this [NDA or supplement] meets [meet] the definition of “new clinical investigation” set forth in § 314.108(a): [List New Clinical Investigations].

Study Number	Phase	Description
Study Number	Phase	Description

This [these] new clinical investigation(s) is [are] an investigation[s] in humans the results of which have not been relied on by FDA to demonstrate substantial evidence of effectiveness of a previously approved drug product for any indication or of safety for a new patient population and do not duplicate the results of another investigation that was relied on by the Agency to demonstrate the effectiveness or safety in a new patient population of a previously approved drug product. *[May include supportive information for this certification.]*

2. Essential to Approval:
  - a. A list of all published studies or publicly available reports of clinical investigations known to the applicant through a literature search that are relevant to the conditions for which the applicant is seeking approval
  - b. [Applicant] has thoroughly searched the scientific literature and, to the best of [Applicant’s] knowledge, the list is complete and accurate and, in [Applicant’s] opinion, such published studies or publicly available reports do not provide a sufficient basis for the approval of the conditions for which the applicant is seeking approval without reference to the new clinical investigation(s) in the [NDA or supplement].

[Include an explanation as to why the studies or reports are insufficient.]

3. Conducted or Sponsored By: [Select as applicable and include appropriate attachments]

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507 [Applicant] is the sponsor named in Form FDA 1571 for IND [IND number]  
508 under which the new clinical investigation(s) that is [are] essential to the approval  
509 of its [NDA or supplement] was [were] conducted.

510  
511 [Applicant] is not the sponsor named in Form FDA 1571 for IND [IND number]  
512 under which the clinical investigation(s) was [were] conducted, but [Applicant]  
513 provided substantial support for the clinical investigation(s) that is [are] essential  
514 to the approval of this [NDA or supplement]. *[Include either a certified statement*  
515 *from a certified public accountant that the applicant provided 50 percent or more*  
516 *of the cost of conducting the study or provide an explanation of why FDA should*  
517 *consider the applicant to have conducted or sponsored the study if the applicant's*  
518 *financial contribution to the study is less than 50 percent or the applicant did not*  
519 *sponsor the investigational new drug.]*

520  
521 [Applicant] is the successor in interest to [predecessor in interest], which is the  
522 sponsor named in Form FDA 1571 for IND [IND number] under which the new  
523 clinical investigation(s) that is [are] essential to the approval of its [NDA or  
524 supplement] was [were] conducted.

525  
526 [Applicant] is the successor in interest to [predecessor in interest], which provided  
527 substantial support for the clinical investigation(s) that is [are] essential to the  
528 approval of this [NDA or supplement].  
529 *[Include either a certified statement from a certified public accountant that the*  
530 *applicant's predecessor in interest provided 50 percent or more of the cost of*  
531 *conducting the study or provide an explanation of why FDA should consider the*  
532 *applicant to have conducted or sponsored the study if the predecessor in interest's*  
533 *financial contribution to the study is less than 50 percent or the predecessor in*  
534 *interest did not sponsor the investigational new drug.]*

535  
536 [Applicant] acquired exclusive rights to the clinical investigation(s) that is [are]  
537 essential to the approval of this [NDA or supplement]. *[Include a copy of the*  
538 *certified statement that the applicant acquired exclusive rights, along with any*  
539 *relevant supportive documentation.]*