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# Guidance for Industry

## New Chemical Entity

### Exclusivity Determinations for

### Certain Fixed-Combination

### Drug Products

#### *DRAFT GUIDANCE*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)**

**February 2014  
Procedural**

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**U.S. Department of Health and Human Services**  
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## Guidance for Industry<sup>1</sup>

# New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products

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## I. INTRODUCTION

The Food and Drug Administration (FDA or the Agency) is issuing this guidance to set forth a change in the Agency's interpretation of the 5-year new chemical entity (NCE) exclusivity provisions as they apply to certain fixed-combination drug products (fixed-combinations). Historically, FDA has interpreted these provisions such that a fixed-combination was ineligible for 5-year NCE exclusivity if it contained a previously approved active moiety, even if the product also contained a *new* active moiety (i.e., an active moiety that the Agency had not previously approved). The Agency recognizes that fixed-combinations have become increasingly prevalent in certain therapeutic areas (including cancer, cardiovascular, and infectious disease) and that these products play an important role in optimizing adherence to dosing regimens and improving patient outcomes. As further discussed below, we are therefore revising our historical interpretation of the 5-year NCE exclusivity provisions to further incentivize the development of certain fixed-combination products.

If the new interpretation is adopted, FDA intends to apply the new interpretation prospectively. Therefore, this guidance does not apply to fixed-combination drug products that were approved prior to adopting the new interpretation.

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

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

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### 41 **II. BACKGROUND**

42  
43 Fixed-combinations are becoming increasingly important from patient and public health  
44 perspectives. Combination therapy is emerging as the standard of care in certain disease settings,  
45 such as cancer, cardiovascular disease, and infectious disease (for example, in human  
46 immunodeficiency virus (HIV) infections/acquired immunodeficiency syndrome (AIDS)). In  
47 recognition of the importance of such combination therapies, FDA has encouraged the  
48 development of these therapies through various policies and initiatives. For example, FDA  
49 recently finalized its guidance for industry titled *Codevelopment of Two or More New*  
50 *Investigational Drugs for Use in Combination* (Codevelopment Guidance).<sup>2</sup> In the  
51 Codevelopment Guidance, FDA explained the potential therapeutic benefits of combination  
52 therapies, including improvement in treatment response, lower risk of developing resistance, and  
53 lower rates of adverse events.<sup>3</sup> We have concluded that a change in our position regarding the  
54 availability of 5-year NCE exclusivity for certain fixed-combinations would further incentivize  
55 the development of these important products.

56  
57 Under the Agency's historical interpretation of the applicable statutory and regulatory  
58 provisions, the presence of a previously approved active moiety in a fixed-combination generally  
59 rendered the drug product ineligible for 5-year NCE exclusivity. This outcome arose out of the  
60 Agency's interpretation of the word *drug* in certain provisions of the Federal Food, Drug, and  
61 Cosmetic Act (FD&C Act) and the term *new chemical entity* in the Agency's implementing  
62 regulations to mean *drug product*.<sup>4</sup> As explained in detail in section III, FDA intends to  
63 interpret *drug* in the relevant provisions to mean *drug substance* or *active ingredient*. This will  
64 allow a drug substance that meets the definition of *new chemical entity*<sup>5</sup> to be eligible for 5-year  
65 NCE exclusivity, even when it is approved in a fixed-combination with another drug substance  
66 that contains a previously approved active moiety. Accordingly, a drug product would be  
67 eligible for 5-year NCE exclusivity, provided that it contains a drug substance that meets the  
68 definition of a *new chemical entity*, regardless of whether that drug substance is approved alone  
69 or in a fixed-combination.

### 70 71 **III. STATUTORY AND REGULATORY FRAMEWORK**

72  
73 Section 505(b) of the FD&C Act (21 U.S.C. 355(b)) establishes the approval requirements for  
74 new drug applications (NDAs). Applications submitted under section 505(b)(1) are supported  
75 entirely by investigations either conducted by the applicant or to which the applicant has a right  
76 of reference. The Drug Price Competition and Patent Term Restoration Act of 1984 (Pub. L. No.  
77 98-417) (the Hatch-Waxman Amendments) amended the FD&C Act and added section 505(b)(2)  
78 and (j) of the FD&C Act. Section 505(b)(2) provides an alternative pathway for approval of an

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<sup>2</sup> See FDA guidance for industry, *Codevelopment of Two or More New Investigational Drugs for Use in Combination*, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm236669.pdf>.

<sup>3</sup> Id. at 2.

<sup>4</sup> See section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act; 21 CFR 314.108(a).

<sup>5</sup> 21 CFR 314.108(a).

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79 NDA, under which some or all of the safety and efficacy investigations relied on for approval  
80 were not conducted by or for the applicant and for which the applicant has not obtained a right of  
81 reference (a 505(b)(2) application). Section 505(j) establishes the abbreviated new drug  
82 application (ANDA) approval process, which provides a more streamlined route for generic  
83 drugs to be approved and brought to market.  
84

85 In addition to establishing the drug approval pathways in section 505(b)(2) and (j) of the FD&C  
86 Act, the Hatch-Waxman Amendments authorized periods of exclusivity intended to provide  
87 incentives for pharmaceutical innovation by protecting certain drugs approved in an NDA from  
88 competition for certain periods. The 5-year NCE exclusivity provision states:  
89

90       If an application submitted under subsection (b) of this section for a drug, no  
91       active ingredient (including any ester or salt of the active ingredient) of which has  
92       been approved in any other application under subsection (b) of this section, is  
93       approved . . . no application may be submitted under this subsection which refers  
94       to the drug for which the subsection (b) application was submitted before the  
95       expiration of five years from the date of the approval of the application under  
96       subsection (b) of this section . . . .<sup>6</sup>  
97

98 Thus, the statute includes clauses describing both eligibility for 5-year NCE exclusivity  
99 (eligibility clause) and the parameters of this exclusivity once it attaches (bar clause). Under the  
100 eligibility clause, a drug is eligible for 5-year NCE exclusivity if it is “a *drug*, no active  
101 ingredient (including any ester or salt of the active ingredient) of which has been approved in any  
102 other [505(b)] application.” The bar clause prevents the submission of any ANDA or 505(b)(2)  
103 application that “refers to the *drug* for which the [505(b)] application was submitted.” This bar  
104 on submission lasts for “five years from the date of the approval of the [505(b)] application.”<sup>7</sup>  
105 Five-year NCE exclusivity does not block the submission, review, or approval of a 505(b)(1)  
106 NDA.  
107

108 In 1989, FDA published a proposed rule (Proposed Rule) interpreting and implementing the 5-  
109 year NCE exclusivity statutory provisions, along with other provisions of the Hatch-Waxman  
110 Amendments.<sup>8</sup> In 1994, FDA finalized the rule (Final Rule) without substantive changes to the  
111 exclusivity-related provisions of the Proposed Rule.<sup>9</sup> The regulations, as finalized, describe 5-  
112 year NCE exclusivity as follows:  
113

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<sup>6</sup> Section 505(j)(5)(F)(ii) of the FD&C Act; see also section 505(c)(3)(E)(ii) of the FD&C Act.

<sup>7</sup> *Id.* A 505(b)(2) application or an ANDA may be submitted after the expiration of 4 years from the date of approval if the 505(b)(2) application or ANDA contains a certification of patent invalidity or noninfringement to a patent listed for the listed drug referenced. This certification is also referred to as a paragraph IV certification. Section 505(j)(2)(A)(vii)(IV) of the FD&C Act; see 21 CFR 314.108(b)(2) and (3); see also section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act.

<sup>8</sup> FDA, “Abbreviated New Drug Application Regulations,” Proposed Rule, 54 FR 28872 (July 10, 1989).

<sup>9</sup> FDA, “Abbreviated New Drug Applications; Patent and Exclusivity Provisions,” Final Rule, 59 FR 50338 (Oct. 3, 1994).

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114 If a drug product that contains a *new chemical entity* was approved . . . in an  
115 application submitted under section 505(b) of the act, no person may submit a  
116 505(b)(2) application or abbreviated new drug application under section 505(j) of  
117 the act for a drug product that contains the same *active moiety* as in the *new*  
118 *chemical entity* for a period of 5 years from the date of approval of the first  
119 approved new drug application . . . .<sup>10</sup>  
120

121 Thus, under 21 CFR 314.108(b)(2), if a drug product contains a *new chemical entity*, then the  
122 Agency is precluded from accepting any ANDA or 505(b)(2) application for a drug product that  
123 contains the same “active moiety as in the new chemical entity” until the 5-year NCE exclusivity  
124 period has expired.  
125

126 This provision includes several terms of art, two of which are defined in 21 CFR 314.108:  
127

- 128 • *New chemical entity* (NCE) is “a drug that contains no active moiety that has been  
129 approved by FDA in any other application submitted under section 505(b) of the act.”<sup>11</sup>  
130
- 131 • *Active moiety* is “the molecule or ion, excluding those appended portions of the molecule  
132 that cause the drug to be an ester, salt . . . , or other noncovalent derivative . . . of the  
133 molecule, responsible for the physiological or pharmacological action of the drug  
134 substance.”<sup>12</sup>  
135

136 In defining these terms, the regulation interprets the statutory phrase “an active ingredient  
137 (including any salt or ester of the active ingredient)” in the eligibility clause to refer to an “active  
138 moiety.”<sup>13</sup> Other terms of art incorporated into this provision of the regulations are defined in 21  
139 CFR parts 210 and 314:  
140

- 141 • *Drug product*, in part, means “a finished dosage form, for example, tablet, capsule, or  
142 solution, that contains a drug substance. . . .”<sup>14</sup>  
143
- 144 • *Drug substance* is “an active ingredient that is intended to furnish pharmacological  
145 activity or other direct effect . . . but does not include intermediates use [sic] in the  
146 synthesis of such ingredient.”<sup>15</sup>  
147
- 148 • An *active ingredient* is “any component that is intended to furnish pharmacological  
149 activity or other direct effect . . . includ[ing] those components that may undergo

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<sup>10</sup> 21 CFR 314.108(b)(2) (emphasis added).

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

<sup>12</sup> Id.

<sup>13</sup> 59 FR 50338 at 50358 (“The agency has concluded that the term ‘active ingredient,’ as used in the phrase ‘active ingredient (including any salt or ester of the active ingredient),’ means active moiety.”).

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

<sup>15</sup> Id.

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150 chemical change in the manufacture of the drug product and be present in the drug  
151 product in a modified form intended to furnish the specified activity or effect.”<sup>16</sup>  
152

153 The preamble to the Proposed Rule further states that “[t]he Agency notes that the term “drug” is  
154 used throughout section 505 of the act. FDA interprets the term ‘drug’ to mean ‘drug product’  
155 unless otherwise specified.”<sup>17</sup>  
156

#### 157 **IV. FDA’S HISTORICAL INTERPRETATION OF THE 5-YEAR NCE** 158 **EXCLUSIVITY PROVISIONS** 159

160 The FD&C Act defines the term *drug* broadly and delegates to FDA the task of determining how  
161 to apply the definition in particular statutory provisions.<sup>18</sup> *Drug* can mean a finished drug  
162 product (articles “intended for use in the diagnosis, cure, mitigation, treatment, or prevention of  
163 disease in man” or “intended to affect the structure or function of the body of man”)<sup>19</sup> or the  
164 component of a finished drug product (“articles intended for use as a [drug] component”).<sup>20</sup>  
165 Therefore, FDA has recognized, and courts have accepted, that *drug* can be interpreted, among  
166 other possible meanings, to mean either *drug product* or *drug substance*.<sup>21</sup>  
167

168 Historically, FDA has interpreted the term *drug* in the eligibility clause of the 5-year NCE  
169 exclusivity statutory provisions to mean *drug product*, not *drug substance*. In 1988, in an  
170 informal letter to industry that predated the issuance of FDA’s implementing regulations, the  
171 Agency stated that it “considers a *drug product* eligible for the five-year period [of NCE  
172 exclusivity] if it contains no active moiety that was previously approved by the Agency” and “a  
173 *drug product* will . . . not be considered a ‘new chemical entity’ entitled to five years of  
174 exclusivity if it contains a previously approved active moiety . . . .”<sup>22</sup>  
175

176 After issuing the Final Rule, FDA continued to interpret the term *drug* to mean *drug product*,  
177 such that a new chemical entity that is eligible for 5-year NCE exclusivity is a *drug product* that

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<sup>16</sup> 21 CFR 210.3(b)(7).

<sup>17</sup> 54 FR 28872 at 28877.

<sup>18</sup> See, e.g., *Pharmanex v. Shalala*, 221 F.3d 1151, 1156 (10th Cir. 2000) (“[T]he term ‘drug’ is defined in [section 201(g) of the FD&C Act (21 U.S.C. 321(g))] to include both finished drug products as well as individual constituents. Thus, the definition of ‘new drug’ is largely colored by the ambiguity that attends the broad term ‘drug.’”). See also *United States v. Sullivan*, 332 U.S. 689, 694 (1948) (“[FDA] is given rather broad discretion [in administering the FD&C Act].”).

<sup>19</sup> Section 201(g)(1)(B) and (C) of the FD&C Act.

<sup>20</sup> Section 201(g)(1)(D) of the FD&C Act.

<sup>21</sup> See, e.g., *United States v. Generix Drug Corp.*, 460 U.S. 453, 459 (1983) (holding that section 201(g)(1) of the FD&C Act is “plainly broad enough to include” both “active ingredient” and “drug product”); *Pfizer, Inc. v. FDA*, 753 F. Supp. 171, 176 (D. Md. 1990) (stating that the definition of drug “covers both a finished ‘drug product’ and its active and inactive ingredient or ingredients.”).

<sup>22</sup> Letter from Carl C. Peck, M.D., Director, Center for Drug Evaluation and Research, to all NDA or ANDA Holders and Applicants, at p. 2 (April 28, 1988) (Peck Letter) (emphasis added), available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075014.pdf>.



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178 “contains no active moiety that has been [previously] approved by FDA.”<sup>23</sup> As the preamble to  
179 the Proposed Rule states, a “drug product will thus not be considered a ‘new chemical entity’  
180 entitled to 5 years of exclusivity if it contains a previously approved active moiety . . . .”<sup>24</sup>  
181 Under this interpretation of the statute and regulations, if an active moiety that has never been  
182 previously approved is approved in an application for a fixed-combination that also includes one  
183 or more active moieties that have been previously approved, that fixed-combination would be  
184 considered a drug product that contains a previously approved active moiety. As such, it would  
185 not be eligible for 5-year NCE exclusivity because it would not be considered a “drug [product]  
186 no [active moiety] of which has been approved in any other application under [section  
187 505(b)].”<sup>25</sup>  
188

189 At the same time, the Agency interpreted the term *drug* in the bar clause to mean *drug substance*.  
190 As explained in the Proposed Rule, after a drug product becomes eligible for 5-year NCE  
191 exclusivity, certain drug products subsequently developed that contain the same active moiety  
192 would also benefit from the original product’s 5-year NCE exclusivity until the exclusivity  
193 period for the original product has expired.<sup>26</sup> Under this policy (known as the umbrella policy),  
194 5-year NCE exclusivity does not attach only to the first approved drug product that was eligible  
195 for 5-year NCE exclusivity, but also to the line of products containing the same active moiety.  
196 FDA explained its reasoning for this interpretation as follows:  
197

198 [T]he agency interprets [5-year NCE exclusivity] to cover any subsequent  
199 approval of an application or supplemental application for a different ester, salt, or  
200 other noncovalent derivative, or a different dosage form, strength, route of  
201 administration, or new use of a drug with the same active moiety. Any  
202 modification to the product will be protected for the period of exclusivity  
203 remaining on the original application, unless the change occurs after or toward the  
204 end of the initial 5 years of exclusivity and independently qualifies for exclusivity  
205 under another exclusivity provision.<sup>27</sup>  
206

207 Accordingly, under the umbrella policy, 5-year NCE exclusivity will apply not just to the first  
208 approved drug product containing no previously approved active moiety, but, with some  
209 exceptions, would also apply to any other drug product developed that contains the same new  
210 active moiety as in the first drug product and that is approved during the 5-year period. Such a  
211 subsequent drug product will be protected for the balance of the 5-year period, which runs from  
212 the date of approval of the first approved drug product.

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<sup>23</sup> 21 CFR 314.108(a).

<sup>24</sup> 54 FR 28872 at 28898.

<sup>25</sup> See section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act. The preamble to the Proposed Rule contains similar language in the context of a 10-year exclusivity provision (54 FR 28872 at 28898) (“A drug product is entitled to 10 years of exclusivity only if it does not contain an active moiety that has been part of a drug product previously approved under section 505(b) of the act either as a single ingredient or as one ingredient of a combination drug product.”).

<sup>26</sup> 54 FR 28872 at 28898-28899.

<sup>27</sup> *Id.*

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### V. REVISED AGENCY INTERPRETATION OF THE 5-YEAR NCE EXCLUSIVITY PROVISIONS

The field of fixed-combination therapy has evolved significantly since the Agency promulgated its 5-year NCE exclusivity regulations. Fixed-combinations have become increasingly common in a diverse set of therapeutic areas, ranging from HIV to cardiovascular disease to cancer. The available data on fixed-combination approvals supports this proposition. In the nearly 20 years since FDA finalized the regulations on exclusivity, the Agency has approved 19 NDAs for fixed-combinations containing at least one new active moiety. More than half of these NDAs have gained approval within the last 7 years. As discussed in section II, in recent years, FDA has adopted policies aimed at encouraging the development of fixed-combinations because, among other things, such combinations have been shown to improve treatment response, lower the risk of developing resistance, and lower the rates of adverse events.

In 2013, the Agency was petitioned to revise its current interpretation of the 5-year NCE exclusivity provisions with respect to certain fixed-combinations.<sup>28</sup> The petitioners made several contentions in support of their conclusion that FDA’s current interpretation of the 5-year NCE exclusivity provisions discourages the development of new active moieties in fixed-combinations with previously approved active moieties. Among other things, the petitioners stated that FDA’s existing interpretation might encourage an applicant to submit an NDA for a single-entity product before it submits an NDA for a fixed-combination to secure 5-year NCE exclusivity for the single entity and protect the later-approved fixed-combination with that exclusivity under the umbrella policy. This might lead to suboptimal drug development strategies, especially in light of the increasing importance of fixed-combinations. In addition, the petitioners stressed that timing the order of approval to preserve exclusivity may not be available in some situations, such as for a new active moiety that may not be effective or safe unless it is marketed in a fixed-combination.

In light of the increasing importance of fixed-combination products to treat serious diseases and conditions, and considering the factors discussed above, FDA has concluded that the new interpretation urged by the petitioners would be beneficial to the public health. Accordingly, FDA is changing its interpretation of the 5-year NCE exclusivity provisions to align the exclusivity incentives more closely with FDA’s public health goals. Under the revised interpretation, the term *drug* in the eligibility clause of the statutory provisions, and in the regulatory definition of *new chemical entity*, refers to *drug substance*, not *drug product*.<sup>29</sup>

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<sup>28</sup> Hogan Lovells, on behalf of Gilead Sciences, Inc., submitted a citizen petition dated January 8, 2013, requesting 5-year NCE exclusivity for cobicistat and elvitegravir, the new active moieties in the fixed-combination Stribild (cobicistat; elvitegravir; emtricitabine; tenofovir disoproxil fumarate) (NDA 203100) (FDA-2013-P-0058). Buchanan Ingersoll & Rooney PC, on behalf of Ferring Pharmaceuticals, Inc., submitted a citizen petition dated January 29, 2013, requesting 5-year NCE exclusivity for picosulfate, the new active moiety in the fixed-combination Prepopik (citric acid; magnesium oxide; sodium picosulfate) (NDA 202535) (FDA-2013-P-0119). Ropes & Gray LLP, on behalf of Bayer HealthCare Pharmaceuticals Inc., submitted a citizen petition dated April 19, 2013, requesting 5-year NCE exclusivity for dienogest, the new active moiety in the fixed-combination Natazia (estradiol valerate; dienogest) (NDA 022252) (FDA-2013-P-0471).

<sup>29</sup> Section 505(c)(3)(E)(ii) and (j)(5)(F)(ii) of the FD&C Act; 21 CFR 314.108(a).

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249 Accordingly, a 5-year NCE exclusivity determination will be made for each drug substance in a  
250 drug product, not for the drug product as a whole. As a result, an application for a fixed-  
251 combination submitted under section 505(b) of the FD&C Act will be eligible for 5-year NCE  
252 exclusivity if it contains a drug substance, no active moiety of which has been approved in any  
253 other application under section 505(b).<sup>30</sup> For example, a fixed-combination drug product that  
254 contains a drug substance with a single, new active moiety would be eligible for 5-year NCE  
255 exclusivity, even if the fixed-combination also contains a drug substance with a previously  
256 approved active moiety.

257  
258 As explained in section IV, this is a permissible construction of the 5-year exclusivity statutory  
259 provisions and implementing regulations because of the inherent ambiguity in the term *drug*.  
260 Because this interpretation represents a change in the Agency’s existing interpretation of the  
261 relevant authorities that is of “more than a minor nature,” the Agency is issuing this draft  
262 guidance document to solicit public comment on the new interpretation described above.<sup>31</sup>

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<sup>30</sup> This change in interpretation generally will not affect 5-year NCE exclusivity determinations for single-entity drug products. Such products typically contain a single drug substance that contains a single active moiety. In such cases, where the drug substance contains a previously approved active moiety, so does the drug product.

<sup>31</sup> See section 701(h)(1)(C) of the FD&C Act (21 U.S.C. 371(h)(1)(C)); 21 CFR 10.115. The Agency does not intend to apply the revised interpretation until this guidance is finalized.