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DRAFT GUIDANCE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
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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.

[1] 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.

II. BACKGROUND

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

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

III. STATUTORY AND REGULATORY FRAMEWORK

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

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[2] 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.

[3] Id. at 2.

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

[5] 21 CFR 314.108(a).

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

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

> If an application submitted under subsection (b) of this section for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application under subsection (b) of this section, is approved . . . no application may be submitted under this subsection which refers to the drug for which the subsection (b) application was submitted before the expiration of five years from the date of the approval of the application under subsection (b) of this section . . . .[6]

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

In 1989, FDA published a proposed rule (Proposed Rule) interpreting and implementing the 5-year NCE exclusivity statutory provisions, along with other provisions of the Hatch-Waxman Amendments.[8] In 1994, FDA finalized the rule (Final Rule) without substantive changes to the exclusivity-related provisions of the Proposed Rule.[9] The regulations, as finalized, describe 5-year NCE exclusivity as follows:

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[6] Section 505(j)(5)(F)(ii) of the FD&C Act; see also section 505(c)(3)(E)(ii) of the FD&C Act.

[7] 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.

[8] FDA, "Abbreviated New Drug Application Regulations," Proposed Rule, 54 FR 28872 (July 10, 1989).

[9] FDA, "Abbreviated New Drug Applications; Patent and Exclusivity Provisions," Final Rule, 59 FR 50338 (Oct. 3, 1994).

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

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

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

- *New chemical entity* (NCE) is "a drug that contains no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act."[11]

- *Active moiety* is "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt . . . , or other noncovalent derivative . . . of the molecule, responsible for the physiological or pharmacological action of the drug substance."[12]

In defining these terms, the regulation interprets the statutory phrase "an active ingredient (including any salt or ester of the active ingredient)" in the eligibility clause to refer to an "active moiety."[13] Other terms of art incorporated into this provision of the regulations are defined in 21 CFR parts 210 and 314:

- *Drug product*, in part, means "a finished dosage form, for example, tablet, capsule, or solution, that contains a drug substance. . . ."[14]

- *Drug substance* is "an active ingredient that is intended to furnish pharmacological activity or other direct effect . . . but does not include intermediates use [sic] in the synthesis of such ingredient."[15]

- An *active ingredient* is "any component that is intended to furnish pharmacological activity or other direct effect . . . includ[ing] those components that may undergo

[10] 21 CFR 314.108(b)(2) (emphasis added).

[11] 21 CFR 314.108(a).

[12] Id.

[13] 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.").

[14] 21 CFR 314.3(b).

[15] Id.

chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect."[16]

The preamble to the Proposed Rule further states that "[t]he Agency notes that the term "drug" is used throughout section 505 of the act. FDA interprets the term 'drug' to mean 'drug product' unless otherwise specified."[17]

IV. FDA'S HISTORICAL INTERPRETATION OF THE 5-YEAR NCE EXCLUSIVITY PROVISIONS

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

Historically, FDA has interpreted the term *drug* in the eligibility clause of the 5-year NCE exclusivity statutory provisions to mean *drug product*, not *drug substance*. In 1988, in an informal letter to industry that predated the issuance of FDA's implementing regulations, the Agency stated that it "considers a *drug product* eligible for the five-year period [of NCE exclusivity] if it contains no active moiety that was previously approved by the Agency" and "a *drug product* will . . . not be considered a 'new chemical entity' entitled to five years of exclusivity if it contains a previously approved active moiety . . . ."[22]

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

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[16] 21 CFR 210.3(b)(7).

[17] 54 FR 28872 at 28877.

[18] 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].").

[19] Section 201(g)(1)(B) and (C) of the FD&C Act.

[20] Section 201(g)(1)(D) of the FD&C Act.

[21] 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.").

[22] 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.

"contains no active moiety that has been [previously] approved by FDA."[23] As the preamble to the Proposed Rule states, a "drug product will thus not be considered a 'new chemical entity' entitled to 5 years of exclusivity if it contains a previously approved active moiety . . . ."[24] Under this interpretation of the statute and regulations, if an active moiety that has never been previously approved is approved in an application for a fixed-combination that also includes one or more active moieties that have been previously approved, that fixed-combination would be considered a drug product that contains a previously approved active moiety. As such, it would not be eligible for 5-year NCE exclusivity because it would not be considered a "drug [product] no [active moiety] of which has been approved in any other application under [section 505(b)]."[25]

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

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

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

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[23] 21 CFR 314.108(a).

[24] 54 FR 28872 at 28898.

[25] 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.").

[26] 54 FR 28872 at 28898-28899.

[27] Id.

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.[28] 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*.[29]

[28] 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).

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

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

As explained in section IV, this is a permissible construction of the 5-year exclusivity statutory provisions and implementing regulations because of the inherent ambiguity in the term *drug*. Because this interpretation represents a change in the Agency's existing interpretation of the relevant authorities that is of "more than a minor nature," the Agency is issuing this draft guidance document to solicit public comment on the new interpretation described above.[31]

[30] 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.

[31] 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.