Biotechnology Industry Organization

April 25, 2014

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA - 2013-D-1675-0001: Draft Guidance for Industry on New Chemical Entity Determinations for Certain Fixed-Combination Drug Products

Dear Sir/Madam:

The Biotechnology Industry Organization (BIO) thanks the Food and Drug Administration (FDA) for the opportunity to submit comments on the Draft Guidance for Industry: New Chemical Entity Determinations for Certain Fixed-Combination Drug Products (Draft Guidance).

BIO represents more than 1,000 biotechnology companies, academic institutions, state biotechnology centers and related organizations across the United States and in more than 30 other nations. BIO members are involved in the research and development of innovative healthcare, agricultural, industrial and environmental biotechnology products, thereby expanding the boundaries of science to benefit humanity by providing better healthcare, enhanced agriculture, and a cleaner and safer environment.

BIO supports FDA's proposed revised interpretation in the Draft Guidance of the term "drug" in the eligibility clause of the New Chemical Entity (NCE) exclusivity statutory provisions. " FDA's revised interpretation, as expressed in the Draft Guidance, is a permissible reinterpretation, and when implemented, will positively impact public health, by encouraging innovation in fixed dose combination drugs. In order to both benefit public health as well as to ensure fair and consistent treatment of fixed dose combination product exclusivity determinations going forward, BIO urges FDA to finalize and implement this new interpretation expeditiously.

Background

As explained in the Draft Guidance, under FDA's historical interpretation of the term "drug" in provisions of the Federal Food, Drug and Cosmetic Act (FD&C Act),[1] the presence of a previously approved active moiety in a fixed combination drug product rendered the drug product ineligible for five-year NCE exclusivity.[2] Specifically, FDA previously interpreted the term "drug" in the relevant statute to mean "drug product" rather than "drug substance." Thus, in FDA's view, all of the ingredients in the drug product were required to be eligible for five-year NCE exclusivity in order for the entire combination drug product to receive five-year NCE exclusivity. In other

[1] 21 U.S.C. § 355(j)(5)(F)(ii).
[2] Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Draft Guidance for Industry: New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products (Feb. 2014) (Draft Guidance), at 2, lines 57-62.

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words, the combination drug was not eligible for five-year NCE exclusivity if it contained one previously approved active moiety, even if it also contained a previously unapproved NCE.[3]

In 2013, FDA received three citizen's petitions requesting the Agency revise its current interpretation of the five-year NCE exclusivity provisions with respect to certain fixed dose combination drugs.[4] The various petitioners requested that FDA recognize five-year exclusivity under sections 505(c)(3)(E)(ii) and 505(j)(5)(F)(ii) of the FD&C Act for the combination drugs containing new active ingredients (that had not been previously approved) combined with a previously approved active ingredient. In general, the various petitioners argued that FDA's interpretation of the relevant provisions of the FD&C Act were out of date, and had not kept pace with the important advances in medicine demonstrated by combination therapies. Petitioners also explained that FDA's historic interpretation discourages the development of new fixed combination drug products with at least one previously approved active moiety. Simultaneous with the publication of this Draft Guidance, FDA rejected all three petitions.[5]

If the Draft Guidance is finalized, FDA would adopt the interpretation urged by the various petitioners. A five-year NCE exclusivity determination will be made for each "drug substance" or active ingredient within a combination drug product. As a result, an application for a fixed combination drug submitted under section 505(b) of the FD&C Act will be eligible for five-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). For example, a fixed combination drug product that contains a drug substance with a single, new active moiety would be eligible for five-year NCE exclusivity, even if the fixed-combination drug also contains a previously approved active ingredient. Accordingly, in this Draft Guidance, FDA is proposing to revise its interpretation, and grant five-year exclusivity for certain fixed-combination drug products that contain both newly applied and previously approved chemical entities.

Comments

BIO supports FDA's proposed interpretation of the statute and regulations, both as an appropriate interpretation of the statute as well as correct public policy. BIO agrees with FDA that making five-year NCE exclusivity available for fixed combinations would incentivize the development of such products, and urges the Agency to implement the revised interpretation as expeditiously as possible. BIO's support for swift implementation of FDA's proposed interpretation should not be construed, however, as agreement with FDA's decision to apply its position going forward only (and thus not applying the reinterpretation to petitioners' applications). Nonetheless, because of the important public health and other benefits represented by the Agency's proposed interpretation, BIO supports rapid Agency finalization of the Draft Guidance.

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[3] Draft Guidance, p. 5, lines 168 – 180, citing the preamble to the Proposed Rule ("drug product will thus not be considered a 'new chemical entity' entitled to 5 years of exclusivity if it contains a previously approved moiety…"), 54 Fed. Reg. 28872, 28898 (July 10, 1989).

[4] See generally, Hogan Lovells, on behalf of Gilead Sciences, Inc., Citizen Petition dated January 8, 2013, ((FDA-2013-P-0058); Buchanan Ingersoll & Rooney PC, on behalf of Ferring Pharmaceuticals, Inc., Citizen Petition dated January 29, 2013, (FDA-2013-P-0119); and Ropes & Gray LLP, on behalf of Bayer HealthCare Pharmaceuticals Inc., Citizen Petition dated April 19, 2013, (FDA-2013-P-0471).

[5] We note that, to date, two of the petitioners have petitioned FDA for reconsideration. See Hogan Lovells, on behalf of Gilead Sciences, Inc., Petition for Reconsideration, dated March 21, 2014 (FDA-2013-P-0058); and Buchanan Ingersoll & Rooney PC, on behalf of Ferring Pharmaceuticals, Inc., Petition for Reconsideration and Petition for Stay, dated March 21, 2014 (FDA-2013-P-0119).

Reinterpretation of Relevant Language

The relevant exclusivity provision of the FD&C Act states:

> (ii) 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 after September 24, l984, 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 approval of the application under subsection (b) of this section….[6]

As FDA explains in the Draft Guidance, FDA has historically interpreted the term "drug" in this section to mean "drug product," thus limiting availability of the exclusivity protections to those combination drug products containing only previously unapproved active ingredients. However, as noted by FDA, there is "inherent ambiguity in the term *drug*,"[7] and the term has been defined by FDA differently in various contexts. As FDA notes in the Draft Guidance, "FDA has recognized, and courts have accepted, that 'drug' can be interpreted, among other possible meanings, to mean either 'drug product' or 'drug substance.'"[8]

With regard to the five-year NCE exclusivity provisions, FDA's historical interpretation was that the term in this context meant "drug product," defined in the regulations as a finished dosage form, and containing a drug substance.[9] Based on that interpretation NCE exclusivity was not available for a new chemical entity/active ingredient submitted for the first time to FDA as part of a combination drug product also containing a previously approved active ingredient.

FDA is now proposing merely to change its interpretation of the term "drug" in the NCE exclusivity provision from "drug product" to "drug substance." "Drug substance" is defined, in part, as "an active ingredient that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease." As explained in detail in the Draft Guidance as well as in the referenced citizen's petitions, in context, the term drug may be read to mean "drug substance," and thus represents a reasonable FDA interpretation.

This interpretation of the term "drug" in the relevant NCE exclusivity provisions of the FD&C Act enables a new active ingredient to be eligible for five-year NCE exclusivity despite its combination with a previously approved active ingredient. Once exclusivity attaches to the previously unapproved active ingredient, exclusivity then attaches to the entire fixed dose combination product, based on the FDA's umbrella approach.[10] BIO supports the Agency's rationale and interpretive outcome.

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[6] 21 USC §355(j)(5)(F)(ii).
[7] Draft Guidance, at 8.
[8] Draft Guidance, at 5.
[9] 21 CFR 210.3(4).
[10] Draft Guidance, at 6.

Biotechnology Industry Organization

Further, BIO also believes that FDA can, and should, implement this new policy immediately, and not – as suggested in the Draft Guidance – by waiting until the Draft Guidance is finalized, and then applying NCE exclusivity to combination products approved from that point.[11] NCE exclusivity is governed by the FD&C Act provisions governing 505(b)(2) applications and ANDAs. It is not a right "awarded to" or held by NDA sponsors from the time of their initial approval; rather, it is simply a statutory prohibition on FDA's acceptance or approval of certain types of applications at certain times.[12]

The fact that FDA may, as a matter of courtesy, inform interested parties through the Orange Book whether 505(b)(2) applications or ANDAs may be impacted by NCE exclusivity in the future does not change how the exclusivity operates. This is, for example, how FDA currently interprets 180-day exclusivity, where the agency declines to make decisions on the existence and impact of the exclusivity unless and until it is faced with the final approval of a later-submitted ANDA.[13] Similarly, here, the existence and impact of any NCE exclusivity is not fixed until FDA is faced with the potential submission of a 505(b)(2) application or ANDA. For this reason, in furtherance of the important public health goals described below, it is entirely appropriate for FDA to begin applying NCE exclusivity immediately – including to recently approved products for which no 505(b)(s) applications or ANDAs have yet been submitted.

Policy Considerations

There are important public health reasons for FDA to revise its interpretation as proposed in the Draft Guidance. As FDA notes throughout the Draft Guidance, the Agency has recently "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."[14] BIO strongly supports FDA's efforts to encourage the development of these important products, and believes that the agency's Draft Guidance is an important step in doing so.

As articulated by the petitioners, and by FDA itself, current policy provides a disincentive for innovation in combination therapies. Exclusivity is intended to encourage innovation by providing limited protection from competition to the owners of a new therapy.[15] The Agency's proposed reinterpretation would correct the situation in which a company that has developed a new active substance, that happens to be best used with other existing drugs, would instead be at a competitive disadvantage. The new interpretation will promote the development of combination drug therapies, and eliminate the current disincentive to combination drug development containing innovative drug substances. Accordingly, BIO urges the Agency to finalize the Draft Guidance as expeditiously as possible.

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[11] Draft Guidance at 1.

[12] *See, e.g.,* 21 USC §355(j)(5)(F)(ii) ("If an application submitted under subsection (b) for a drug, no active ingredient . . . of which has been approved in any other application under subsection (b), is approved after the date of enactment of this subsection, *no application may be submitted* under this subsection which refers to the drug for which the subsection (b) application was submitted . . . .) (emphasis added).

[13] Beyond 180-day exclusivity, there are numerous other examples of FDA awarding, modifying, or even abrogating exclusivity rights after approval of the underlying applications.

[14] Draft Guidance at 7.

[15] FDA, Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069962.htm (last accessed April 21, 2014).

Thank you for your attention to this matter, and we would be pleased to provide further input or clarification of our comments, as needed.

Sincerely,

/S/

Jeffrey Peters
Deputy General Counsel, Health
Biotechnology Industry Organization (BIO)