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FDA Draft Guidance Proposes Change to Combination Product Exclusivity Policy

New market exclusivity opportunities emerge for pharmaceutical companies.

In draft guidance released by the Food and Drug Administration (FDA or the Agency) on February 24, 2014, the Agency proposed changes to its exclusivity policy for fixed-combination drug products. If implemented, the guidance would provide five years of market exclusivity, rather than three years, to fixed-combination drug products that include both new and previously approved active moieties. The change will have significant effects on life cycle management strategies, corporate partnering activities, and the science around fixed-combination products, breathing new life into the value of some old drugs.

Statutory Five-Year Exclusivity Provision

Under the Federal Food, Drug, and Cosmetic Act (FFDCA), sponsors of certain drug products can receive periods of market exclusivity granted by FDA that are in addition to the patent protection the products might otherwise have. Market exclusivity is intended to encourage innovation by protecting the owners of new drug applications (NDAs) from competition for prescribed periods of time.[1] During these periods of time, FDA is prevented from approving and, in some cases, receiving applications submitted under section 505(b)(2) of the FFDCA and abbreviated new drug applications (ANDAs) that refer to the approved drug substance.[2]

One form of exclusivity is the five-year new chemical entity (NCE) exclusivity. The FFDCA provides the following:

> If a [full NDA or 505(b)(2) application] for a drug, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other [full NDA or 505(b)(2) application], is approved . . . , no [505(b)(2) application or ANDA] may be submitted . . . which refers to the drug for which the [original] application was submitted before the expiration of five years from the date of the approval of the application. . . .[3]

This provision was added to the FFDCA through the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Amendments.[4]

Prior Five-Year Exclusivity Interpretation

In an April 1988 letter to all NDA and ANDA holders and applicants, the FDA stated that, "The five-year period of exclusivity is available only to new chemical entities. The Agency considers a *drug product* eligible for the five-year period if it contains no active moiety that was previously approved by the Agency."[5] This letter further specified that new chemical entities are *drug products* that do not contain previously approved active moieties.[6]

FDA's choice of the words "drug product" in this letter was significant. The statutory exclusivity provisions did not make reference to "drug products." Rather, the provision states that five-year exclusivity is available to "*a drug*, no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other [full

1. FDA, Small Business Assistance: Frequently Asked Questions for New Drug Product Exclusivity, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069962.htm (last visited Feb. 24, 2014).

2. *Id.*

3. FFDCA §§ 505(j)(5)(F)(ii), 505(c)(3)(E)(ii).

4. FDA, Small Business Assistance, *supra* note 1.

5. Letter from Carl C. Peck, M.D., Dir., Ctr. for Drug Evaluation & Research, to all NDA or ANDA Holders and Applications at 2 (Apr. 28, 1988) (emphasis added), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075014.pdf.

6. *Id.*

NDA or 505(b)(2) application.]"[7] "Drug," as defined by the FFDCA, includes both finished drug products and components of finished products.[8] Thus, the five-year exclusivity provision could be read to cover individual active ingredients or the drug product as a whole. By restricting the term "drug" to only "drug products," the Agency narrowed the availability of the five-year exclusivity provision to only finished products for which no active moieties had previously been approved. This excluded combination products that contained both new active moieties and previously approved active moieties from receiving five-year exclusivity. Such products, under FDA's interpretation, were only eligible for three years of market exclusivity.[9]

This interpretation was carried into FDA's 1994 implementing regulations.[10] FDA further defined an active moiety 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."[11] Here again, FDA stated that the term "drug" was limited to "drug products," restricting the availability of the five-year exclusivity to drug products that contained no previously approved active moiety.[12]

Rise of Fixed-Combination Drug Products and FDA's Changing Statutory Interpretation

In the years following FDA's interpretation of the five-year NCE exclusivity provision of the FFDCA, fixed-combination products have become increasingly important in therapeutic treatment for HIV, cardiovascular disease, tuberculosis, and cancer.[13] As stated by FDA, in the last 20 years, it approved 19 NDAs for fixed-combination products containing at least one new active moiety, more than half of which were approved within the last seven years.[14] FDA also adopted policies to encourage the development of fixed-combination products, including its recent guidance on the co-development of combination products.[15] This reflects the Agency's acknowledgement of the increasing importance of fixed-combination products in the treatment of serious diseases and conditions.[16]

At this same time, however, sponsors of fixed-combination products containing previously approved active moieties were not eligible for five years of market exclusivity. Accordingly, in 2013, three different sponsors of fixed-combination products that contained both new and previously approved active moieties filed Citizen Petitions with FDA requesting that it change its interpretation of the five-year exclusivity provision.[17] As stated by the petitioners and echoed in FDA's draft guidance, the five-year exclusivity policy created a disincentive for sponsors to first pursue development of fixed-combination products.[18] Rather, FDA's interpretation encouraged applicants to submit NDAs for single-entity products before submitting the NDA for a fixed-combination product to secure the five-year NCE exclusivity.[19]

In response to these Citizen Petitions, and through its recently released draft guidance, FDA proposed changing its exclusivity policy.[20] If implemented, the proposed policy would reinterpret "drug" within the statutory exclusivity

7. FFDCA §§ 505(j)(5)(F)(ii), 505(c)(3)(E)(ii) (emphasis added).

8. FFDCA § 201(g).

9. FFDCA § 505(c)(3)(E)(iii), 505(j)(5)(F)(iii).

10. 21 C.F.R. § 314.108(a).

11. *Id.*

12. Abbreviated New Drug Application Regulations, 54 Fed. Reg. 28,872, 28,877 (Jul. 10, 1989).

13. FDA, Draft Guidance for Industry: New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products at 6 (Feb. 2014), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM386685.pdf; FDA, FDA-2013-P-0058, FDA-2013-P-0019, FDA-2013-P-0471 Citizen Petition Response at 14 (Feb. 21, 2014) *available at* http://www.regulations.gov/#!documentDetail;D=FDA-2013-P-0471-0006.

14. *Id.*

15. FDA, Guidance for Industry: Codevelopment of Two or More New Investigational Drugs for Use in Combination (June 2013), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM236669.pdf..

16. FDA, Draft Guidance for Industry, *supra* note 13 at 7.

17. Citizen Petition Response, *supra* note 13.

18. FDA, Draft Guidance for Industry, *supra* note 13 at 7.

19. *Id.*

20. *Id.* at 8.

provision and regulation to refer to a "drug substance" or "active ingredient" rather than a "drug product."[21] Accordingly, a drug product would be eligible for five years of exclusivity if it contains any drug substance that contains no active moiety that has previously been approved by the Agency.[22] This would mean that sponsors of a full NDA or 505(b)(2) application for a fixed-combination product would, for the first time, be eligible for five years of market exclusivity if the product contains a previously unapproved active moiety, even if the combination product also included a drug substance with a previously approved active moiety.[23]

New Life for Older Drugs and Other Implications

This revised FDA policy, if implemented, could create significant new opportunities for the drug industry. It will accelerate medical innovation in the area of fixed-combination products by making them eligible for the longer five-year exclusivity. Increased fixed-combination product development efforts would also benefit patients because this could potentially provide access to drugs that are more effective or safer and/or that present a better compliance profile. However, the Agency's decision to implement such a significant policy change through a guidance document, and without formal rulemaking, may elicit legal challenges to the change from manufacturers of recently or nearly approved drug products. Transition provisions may be necessary to create a sense of fairness in the industry. In addition, it is necessary to quickly adopt the guidelines to prevent a short-term chill in the submission of applications for fixed-combination products and to wait out the adoption by FDA to capture the longer exclusivity. Moreover, there will likely be other consequences of the new policy, including the following:

- Requiring companies with existing co-development agreements to review them to ensure that they reflect the new eligibility rules for fixed-combination products
- Creating new co-development opportunities for older, previously approved drugs
- Possibly expanding and increasing the speed of development of metrics and protocols for testing fixed-combination products
- Increasing the consideration of fixed-combination products in life cycle–management strategies
- Likely resulting in the expanded use of 505(b)(2) NDAs
- Possibly resulting in the increased involvement of the generic pharmaceutical companies in drug development as they consider strategies to maximize the value of approved older drugs

Pharmaceutical Research and Manufacturers of America and Biotechnology Industry Organization will likely submit comments, but FDA is also interested in hearing from individual companies by April 25, 2014.

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21. Draft Guidance for Industry on New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products; Availability, 79 Fed. Reg. 10.167, 10,168 (Feb. 24, 2014).

22. *Id.*

23. *Id.;* FDA, Draft Guidance for Industry, *supra* note 13 at 8.