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Amarin Decision Opens Door To Longer Exclusivity Periods

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On May 28, 2015, the U.S. District Court for the District of Columbia vacated and remanded the U.S. Food and Drug Administration's administrative decision denying five years of new chemical entity exclusivity for Amarin Pharmaceuticals Ireland Ltd.'s recently approved drug, Vascepa.[1] With the caveat that the district court's holding is subject to a potential appeal, Amarin is an important case for innovator pharmaceutical companies that are developing drugs that contain, as their sole active ingredient, a single component of a previously FDA-approved active ingredient multicomponent drug mixture, especially if the mixture is not fully characterized.

Background

In the U.S., there are two primary ways that drugs can be protected from generic competition: (1) patents; and (2) FDA market exclusivities. For small molecule drugs, the FDA typically grants, upon approval of a new drug application (NDA), either five-year new chemical entity (NCE) market exclusivity or three-year exclusivity for a new indication, dosage regimen or dosage form for a previously approved drug where clinical data is used as the primary basis for the approval.[2] Although the difference between three and five years seems small at first glance it is not.

If a drug is granted NCE exclusivity, an abbreviated new drug application (ANDA) for a generic version of the drug cannot be approved by the FDA — and therefore cannot be legally marketed — during the five-year exclusivity period.[3] In addition, absent a paragraph IV certification,[4] the FDA cannot even accept a generic drug manufacturer's ANDA for review until the five-year NCE exclusivity period has expired. After an ANDA is filed, the average time to FDA approval is about 35 months.[5] Thus, even without any patents, a drug having five-year NCE exclusivity should enjoy about eight years of market exclusivity.

Conversely, for a drug that has been granted three-year market exclusivity, the FDA can accept an ANDA from a generic manufacturer anytime within the three-year exclusivity period. Thus, a generic drug manufacturer who submits its ANDA one day after the FDA grants three years of market exclusivity for the reference listed drug could potentially have its generic drug on the market the day after the three-year exclusivity expires.[6] Thus, in practice, the difference between three-year exclusivity and five-year NCE exclusivity can actually amount to a difference of five years of market exclusivity, not two years.

Amarin

Amarin initiated development of eicosapentaenoic acid ethyl ester ("EPAe") for the reduction of triglyceride levels in adults with severe hypertriglyceridemia. Amarin sought five-year NCE exclusivity for EPAe, notwithstanding that EPAe was a component in the FDA-approved drug Lovaza.

In the Hatch-Waxman Act, Congress provided that drugs with new active ingredients would be entitled to receive five-year NCE exclusivity. In 2004, the FDA approved Lovaza, whose active ingredient was a mixture of omega-3 esters, including EPAe. Although "portions of Lovaza's label refer to the specific components of the mixture, there is no dispute that its sole 'active ingredient' is the mixture as a whole."[7] Supporting the proposition that Lovaza's mixture-equals-active-ingredient, the FDA, in a recent citizen petition response, "explained that because the Lovaza mixture has not been 'fully characterized,' the FDA has identified the 'entire fish oil mixture as the active ingredient of Lovaza.'"[8] The FDA also explained that "when naturally derived mixtures are not sufficiently characterized to precisely identify every molecule that meaningfully contributes to the activity of the mixture it is difficult to define the active ingredient in terms of the specific components of [the] mixture."[9]

Based on its reading of the statute and the FDA's regulations, Amarin contended that EPAe had never been previously approved by the FDA as an active ingredient. Amarin argued that Lovaza's mixture-as-active-ingredient was different from EPAe as a sole active ingredient for purposes of determining exclusivity. Amarin concluded that if EPAe received approval from the FDA, it should be entitled to five-year NCE exclusivity.

Months after Amarin's EPAe was approved as the drug Vascepa, the FDA denied NCE exclusivity based on a new 'one-to-many' framework analysis.[10] This one-to-many framework, used without previous notice and comment rule-making or guidance, did not perform the 'active ingredient' to 'active ingredient' comparison as required by statute. Instead:

Under that [one-to-many] framework, the FDA "generally" considers component molecules of a mixture to be previously approved "active moieties for purposes of determining a subsequent drug's eligibility for five-year exclusivity where[:] (1) specific molecules in the mixture have been identified; (2) those specific molecules are "consistently present in the mixture"; and (3) those molecules are "responsible at least in part for the physiological or pharmacological action of the mixture, based on a finding that they make a meaningful contribution to the activity of the mixture." The determination of whether a particular molecular component of a previously approved mixture meets these criteria is based on "technological tools and scientific concepts available" at the time the FDA evaluates the exclusivity of a new drug — not the understanding that the FDA had when it approved the mixture in the first place.[11]

Chevron and APA Analysis

Amarin appealed the FDA's administrative decision. On appeal, the district court analyzed the FDA's regulations under two well-known tests: the (1) Chevron standard[12] and (2) Administrative Procedure Act's "arbitrary, capricious, abuse of discretion or otherwise not in accordance with the law" standard.[13]

The district court found that the FDA's one-to-many interpretation failed both tests for a variety of reasons, including three violations of basic rules for interpreting statutes and because the FDA's actions were not reasonable (e.g., they were arbitrary and capricious). Quoting the district court: The "problems

with the FDA's decision are characterized as failures under Chevron step one, step two or the APA's requirement of reasoned decision-making, [and] the [a]gency's decision must be set aside."[14]

Recommendations

With patents being challenged earlier and more often, including in inter partes review proceedings at the U.S. Patent and Trademark Office, exclusivities, which are distinct from the protection provided by patents, are increasingly important to innovating pharmaceutical companies. Five-year NCE exclusivity is significantly more advantageous than three-year exclusivity. Thus, innovators developing single molecule drugs which contain, as their sole active ingredient, a single component of a previously approved active ingredient multicomponent mixture should attempt to gain five-year NCE exclusivity, especially in situations where the multicomponent mixture is uncharacterized or poorly characterized. Steps toward achieving this goal include requesting five-year NCE exclusivity from the FDA, engaging often with the FDA to ensure its thinking on exclusivity is aligned with the innovator's thinking and the law, and being prepared to challenge the FDA both before, and if necessary after, NDA approval, if five years of NCE exclusivity is not granted.

Finally, innovators should make certain that, upon NDA approval, relevant patents are timely listed in the Orange Book so that innovators will be able to take full advantage of the protections afforded by Hatch-Waxman and five-year NCE exclusivity.

Conclusion

In light of Amarin, innovators developing single compounds that are components of previously approved mixtures or combination products should proactively seek, where appropriate, five-year NCE exclusivity. In doing so, innovators should be prepared to challenge any contrary position taken by the FDA based on how a multicomponent drug mixture has been previously characterized and approved by the law.

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[1] Amarin Pharmaceuticals Ireland Ltd. v. FDA, 14-cv-00324 (Dist. Court, Dist. of Columbia, 2015).

[2] This article does not address e.g., orphan drug exclusivity, pediatric exclusivity or Generating

Antibiotics Incentives Now Act exclusivity, because these exclusivities are not directly relevant to the Amarin case.

[3] See 21 U.S.C. §§ 355(c)(3)(E)(ii) and 355(j)(5)(F)(ii).

[4] See 21 U.S.C. § 355(j)(5)(B)(iv).

[5] See B. Pollack, "June Approval Times for ANDAs — A Snapshot in Time," last accessed May 31, 2015.

[6] The three-year and five-year scenarios above are simplified for illustrative purposes and do not take into account the effect of, e.g.: (1) any 30-month litigation stay and (2) the blocking effects of patents which can temporally run beyond FDA exclusivities.

[7] Amarin at page 8 (emphasis added).

[8] Id. (Emphasis added; citation omitted.)

[9] Id.

[10] Id.

[11] Id. at page 13 (citations omitted.)

[12] Chevron USA v. Natural Resources Defense Council, 467 U.S. 837 (1984).

[13] 5 USC § 706(2)(A).

[14] Amarin at page 39.
