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FDA Is Evolving on Qualifications for 'New Chemical Entity'

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When can an old compound be considered new again? Apparently, when the U.S. Food and Drug Administration says so, of course. On May 31, 2016, the FDA awarded Amarin Pharma Inc. five years of new chemical entity (NCE) exclusivity for Vascepa,[1] overturning their previous rejection of NCE exclusivity due to a District of Columbia decision, which vacated and remanded the FDA's administrative decision.[2] The Amarin case highlights the complexity of determining whether certain drugs that contain a previously FDA-approved active ingredient will be considered a new chemical entity.

There are now three relatively recent examples of the FDA having been asked to modify its policy as it relates to NCE status: (1) where the previously approved active moiety is combined with a new chemical entity in a fixed dose combination; (2) where the subject active moiety is part of a previously approved multicomponent drug mixture; and (3) when the same components (i.e. active moieties) have been previously approved, but in a different ratio. On the flip side, FDA appears to be taking a stricter view of the core pharmacophore of an active ingredient by stating that esters (whether stable or labile) of a previously approved active moiety are not eligible for NCE status. Below, we explore how the FDA has been evolving its determination of what qualifies for NCE exclusivity.

What Does It Mean to Have NCE Exclusivity?

FDA marketing exclusivity is a statutory right provided by the Federal Food, Drug and Cosmetic Act under Sections 505(c)(3)(E), granting certain exclusive marketing rights upon approval of a drug. Such exclusivity is independent of and may run concurrently with any patent exclusivity. NCE exclusivity of five years is awarded to drugs that contain "no active moiety that has been approved by FDA in any other application submitted under section 505(b) of the act."[3] If not entitled to NCE exclusivity, the drug may be granted "clinical investigation" exclusivity if new clinical investigations are conducted or sponsored by applicant and are essential for approval.[4]

Obtaining NCE status can be critical to commercialization because it controls the timing of a challenge by generic companies and ensures commercial exclusivity from generic competition. If a drug is granted NCE exclusivity, an abbreviated new drug application or 505(b)(2) application cannot be approved by the FDA during the five-year exclusivity period. In addition, absent a paragraph IV certification, the FDA cannot accept a generic drug manufacturer's ANDA/505(b)(2) application until the five-year NCE exclusivity period has expired. Furthermore, if

a drug has Orange Book-listed patents, though an ANDA may be filed as early as the fourth year, if a paragraph IV certification suit is filed within 45 days, a 30-month stay will be awarded whereby no ANDA or 505(b)(2) application may be approved until the end of the seven and a half year period from the date of approval of the NCE drug.

What Is All the Fuss About Active Moiety?

According to the FDA's regulations, NCE exclusivity is awarded to drugs that contain "no active moiety that has been approved by FDA."[5] However, under the FDCA, drugs with active ingredients[6] that have not been previously approved would be entitled to five-year NCE exclusivity.[7] The statute thus requires a one-to-one correlation of one active ingredient to one active moiety. This is the crux of the Amarin issue.

The Vascepa Story

Vascepa contains icosapent ethyl, which is the ethyl ester of eicosapentaenoic acid (EPA). The FDA approved Vascepa on July 26, 2012 under NDA 202057.[8] On Feb. 21, 2014, the FDA determined that Vascepa was not eligible for five-year NCE exclusivity based on the previous approval of Lovaza. Lovaza is a mixture of about seven ethyl esters of omega-3-fatty acids, principally EPA and docosahexaenoic acid (DHA). Notably, in its approval of Lovaza, the FDA stated that the entire mixture is the active ingredient because the mixture was not sufficiently characterized.[9]

In denying NCE exclusivity for Vascepa, the FDA rejected the "one-to-one" framework used in single molecule drugs and, instead, for the first time, without notice, applied a "one-to-many" approach for well-characterized mixtures, stating that "[i]n cases where at least part of the mixture is well characterized and some components of the mixture that are consistently present and active are identifiable or have been identified, … the entire mixture is the single active ingredient, but that active ingredient may contain more than one component active moiety." In essence, though the FDA had previously conceded that the active ingredient in Lovaza was the entire fish oil mixture, the FDA argued that the active moieties of the Lovaza mixture included both EPA and DHA.

Amarin appealed the FDA's rejection of NCE exclusivity to the U.S. District Court of the District of Columbia. The court vacated and remanded the FDA's decision denying NCE exclusivity and rejected the FDA's "one-to-many" approach as inconsistent with the statute.[10] On May 31, 2016, the FDA finally issued an exclusivity determination concluding that Vascepa has been granted the five-year NCE exclusivity, stating that due to the "multiple factors unique to the matter" and in light of the opinion, the FDA has decided to adopt the "one-to-one" framework in this case.[11]

Extension of Amarin to Other Mixtures

In Amarin, the FDA conceded that for poorly characterized mixtures, the entire mixture should be characterized as the active moiety and that NCE exclusivity would be available for new, poorly characterized mixtures.[12] Under the Amarin decision, even if the mixture is "well-characterized," the "FDA is free to determine whether any particular naturally derived mixture is better understood as containing one or multiple active ingredients."[13]

Omthera Pharmaceuticals Inc., a wholly owned subsidiary of AstraZeneca PLC, is attempting to extend the logic of Amarin to its product, Epanova, a naturally derived mixture including EPA and DHA. The FDA approved Epanova

on May 5, 2014, and lists omega-3-carboxylic acids as the active ingredient.[14] The FDA has denied Epanova NCE exclusivity. After the Amarin decision, Omthera submitted a supplement to their Oct. 31, 2014, citizen petition challenging the FDA's denial, arguing that, under Amarin, "when FDA approves a naturally derived mixture as a single active ingredient product, the agency cannot later treat its components as individual active moieties for exclusivity purposes. Rather, the mixture itself is the active ingredient and, to the extent applicable, the active moiety. If FDA has not previously approved a product that consists of the same mixture, then the new mixture must be awarded 5- year exclusivity."[15] The FDA has yet to act on this citizen petition.

What Other 'Old' Compounds May Be Eligible for NCE Exclusivity?

We explore below the FDA's treatment of other "old" compounds, which may be able to secure NCE exclusivity, including fixed-dose combinations, prodrugs and enantiomers.

Fixed-Dose Combinations

The FDA had traditionally interpreted the statute and regulations as providing for NCE exclusivity only if all drug substances in the fixed-combination product are "new." However, under a new guidance promulgated on Oct. 10, 2014, the FDA re-evaluated its interpretation and stated that fixed-dose combination products could qualify for a five-year NCE exclusivity period as long as any drug substance in the fixed-dose combination product is new.[16] Examples of FDCs that have been awarded NCE status under this new interpretation include Gilead's Harvoni (ledipasvir and sofosbuvir), and Eisai's Akynzeo (netupitant and palonosetron).[17]

Enantiomers

The FDA had initially taken the position that the agency would not grant NCE exclusivity for an enantiomer when the racemate had previously been approved.[18] However, in the 2007 Food and Drug Administration Amendments Act, Congress passed a change in the law that allows award of NCE exclusivity under new §505(u) for enantiomers not previously approved, where the enantiomer is approved for new indications in a different therapeutic class. This NCE exclusivity comes with certain requirements, including label restrictions. On July 25, 2013, Fetzima (levomilnacipran), a stereoisomer of the previously approved racemate, milnacipran HCl (Savella), became the first enantiomer drug to be granted NCE exclusivity under FDA §505(u).

Non-Ester Prodrugs

Vyvanse (lisdexamfetamine dimesylate) is a prodrug of dextroamphetamine (aka Adderall, a previously approved drug). The FDA approved Vyvanse on December 10, 2007 and granted NCE status along with five years of market exclusivity. Generic drugmaker Actavis sued the FDA over this decision, arguing that the active moiety inquiry should identify the specific molecule, or portion of the molecule, responsible for the physiological or pharmacological action, and then treat that molecule as the active moiety.[19] Actavis thus asserted that dextroamphetamine, as the molecule responsible for the pharmacological action of lisdexamfetamine, is the active moiety in Vyvanse and should not be accorded NCE status.

In reaffirming its decision to grant NCE exclusivity, the FDA articulated a structure-centric interpretation of "active moiety" (rather than an activity-based interpretation) under which a drug is classified as an NCE regardless of

which portions of the active ingredient contribute to the overall therapeutic effect of the drug.[20] The D.C. Circuit upheld the FDA's determination.[21]

Thus, the FDA's bright-line structure-centric interpretation of the "active moiety" turns a blind eye to any activity-based arguments for prodrugs exhibiting covalent derivatives. Esters, another type of covalent derivative, are, however, treated differently as seen below.

Esters

The FDA's default position is that NCE exclusivity will not be awarded to a new ester of a previously approved active moiety/ingredient because most ester linkages are rapidly cleaved in vivo to provide the de-esterified molecule.[22] Nevertheless, previously, the FDA had stated that, in exceptional cases, it could award NCE exclusivity to "[a]n ester that is stable, both in vitro and in vivo, is considered to be the active moiety, because the deesterified molecule is devoid of activity."[23]

However, when Veramyst (fluticasone furoate), an ester of Flonase (fluticasone propionate), was approved,[24] GlaxoSmithKline LLC, the sponsor, argued that "the furoate group remains an integral part of this new chemical entity while exerting therapeutic activity at the site of action, and reviewers should appreciate that neither fluticasone furoate nor fluticasone pripionate is ever metabolized to fluticasone." The FDA rejected this activity-based argument and set forth the structure-centric approach articulated in the Vyvanse decision to determine that fluticasone furoate is not entitled to NCE exclusivity.[25] Thus, under the FDA's bright-line structure-based analysis, even if a novel ester appendage can fundamentally change the pharmacokinetics or pharmacodynamics of a previously approved drug, the entire linked molecule will not be eligible for NCE exclusivity.

Conclusion

As discussed above, the prior approval of a drug containing an active ingredient of the innovator drug is not necessarily a death knell for NCE exclusivity. Where, as for Vascepa, the sole active ingredient was previously approved as a mixture and the active ingredient of the mixture is not well characterized, the FDA may confer NCE status to the sole ingredient. Furthermore, NCE status may be conferred on enantiomers, prodrugs, and fixed dose combinations. Given the recent evolution, it is prudent to review the court and FDA decisions to devise a strategy to try to obtain NCE exclusivity.

Endnotes

1 See http://investor.amarincorp.com/releasedetail.cfm?ReleaseID=973501.

2 *Amarin Pharms Ireland Ltd. v. FDA*, 14-cv-00324 (Dist. Court, Dist. of Columbia, 2015).

3 Id.

4 21 CFR 314.108(b)(4). This article does not address other available exclusivities such as e.g., orphan drug exclusivity, pediatric exclusivity, or GAIN Act exclusivity, because these exclusivities are not directly relevant to procuring NCE exclusivity.

5 See 21 CFR 314.108(a).

6 See 21 CFR § 210.3(b)(7).

7 21 U.S.C. 355(c)(3)(E)(ii).

8 FDA, NDA Approval Letter dated July 26, 2012, available here: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202057Orig1s000Approv.pdf.

9 See FDA, NDA Approval Letter dated November 10, 2004 available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-654_Omacor_Approv.pdf; See also FDA letter of November 1, 2004 available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2004/21-654_Omacor_AdminCorres_P1.pdf.

10 *Amarin Pharms Ireland Ltd. v. FDA*, 106 F.Supp.3d 196 (Dist. Court, Dist. of Columbia, 2015).

11 FDA, NCE status Approval Letter dated May 31, 2016 available here: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202057Orig1s000AdminCorresedt3.pdf.

12 See Amarin at page 206.

13 See id.

14 FDA, NDA Approval Letter dated May 5, 2014.

15 AstraZeneca's Supplement to its citizen petition dated November 3, 2015 accessible here: https://www.regulations.gov/document?D=FDA-2014-P-1796-0007.

16 Guidance for Industry – New Chemical Entity Exclusivity Determinations for Certain Fixed-Combination Drug Products accessible at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM386685.pdf (published October 10, 2014; last accessed July 19, 2016).

17 Gilead's Harvoni includes sofosbuvir, a drug approved in 2014 and marketed as Sovaldi. Eisai's Akynzeo includes oral palonosetron, approved in 2008 under the brand name Aloxi.

18 See 59 Fed. Reg. 50,338-50,359 (Oct. 3, 1994).

19 *Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 765 (D.C. Cir. 2010).

20 FDA letter to Shire Development, Inc dated October 23, 2009, Docket No. FDA-2009-N-0184; see also 54 Fed. Reg. at 28898 and Exclusivity Determination for Emend available here: http://www.accessdata.fda.gov/drugsatfda_docs/NDA/2008/022023s000_AdminCorres_P2.pdf.

21 See *Actavis Elizabeth LLC*, 625 F.3d at 765.

22 See 21 CFR 314.108(a).

23 Draft Manual of Policies and Procedures (MAPP) 7500.3 “Drug and Application Classification.”

24 Approved on April 27, 2007 under NDA 022051.

25 FDA letter regarding exclusivity dated 5/29/2012.

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