UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

AMARIN PHARMACEUTICALS IRELAND LTD.,	)	
	)	
Plaintiff,	)	
	)	
v.	)	No. 1:14-cv-00324-RDM
	)	
FOOD AND DRUG ADMINISTRATION, *et al*.,	)	
	)	
Defendants.	)	
	)	

SUPPLEMENTAL MEMORANDUM IN RESPONSE TO THE COURT'S QUESTIONS RAISED AT SUMMARY JUDGMENT HEARING

Defendant Food and Drug Administration ("FDA") makes this filing to provide answers in response to questions raised by the Court at the hearing on March 17, 2015.

1) Has FDA evaluated and approved multiple active ingredients in a single drug product, other than fixed-dose combination products?

Yes. In the Vascepa letter decision, FDA discussed drug products containing the naturally derived mixtures menotropins, which contain more than one active ingredient. *See* FDA Letter at 15-16. Fixed-dose combination products, of which there are many, are the only other situation, to FDA's knowledge, in which FDA approves multiple active ingredients that are then labeled as such on the product.

2) Were the studies cited in FDA's response letter suggesting that EPA independently lowers triglyceride levels relied on by the sponsor when seeking approval of Lovaza?

No. Because approval of Lovaza was sought based on the entire mixture, the supporting studies tested the entire mixture rather than individual components. However, the numerous clinical studies of EPA alone that were cited in FDA's response letter, concluding that EPA causes a significant decrease in serum triglyceride levels, predated the approval of Lovaza (and Vascepa). *See* FDA Letter at 2-3. Further, Lovaza's labeling emphasizes the importance of

EPA's contribution to the pharmacological effect of the drug. *See id.* at 3. Thus, given the timing of the published literature on the subject, it is likely that the Lovaza sponsor was aware of such studies when submitting the Lovaza application.

3) Can FDA identify any further information in the record regarding the new chemical entity ("NCE") exclusivity determination for Qutenza?

The record for this case does not contain a clear basis for the NCE exclusivity determination regarding Qutenza. Importantly, FDA's patent term extension determination with regard to Qutenza is not relevant to FDA's NCE exclusivity determination, because a determination of "active ingredient" for purposes of the statute governing patent term extensions does not require identification of an active moiety. *See* FDA Letter at 21. In its memorandum recommending denial of 5-year NCE exclusivity to Vascepa, the FDA Exclusivity Board mentioned the grant of NCE exclusivity to Qutenza, stating, "Although we are still reviewing the issue, it is possible that this represents a scenario similar to the NCE determination for podofilox where the Agency was not certain about the activity of podofilox in older, previously approved mixtures." *See* Joint App. Tab 2, AR00047, n. 107. Because the issue was not relevant to the Vascepa exclusivity question before it, this is the only mention of Qutenza made by the FDA Exclusivity Board in this memo.

4) Did FDA ever explicitly find that "active ingredient (including any ester or salt of the active ingredient)" is ambiguous so that its regulation, 21 C.F.R. § 314.108, is needed?

In the Federal Register notice announcing the proposed rule that would become the regulation, FDA explained:

> "New chemical entity" means a drug that contains no active moiety that has been approved by the Food and Drug Administration in any other application submitted under section 505(b) of the act. Thus, FDA interprets the statutory requirement that a drug (new chemical entity) contain "no [previously approved] active ingredient (including any ester or

> salt of the active ingredient)" to mean that the drug must not contain any previously approved active moiety. FDA bases this interpretation on the statutory language and on the definition of a "new molecular entity" or "Type 1" drug in FDA's IND/NDA classification scheme (which is used to classify new drugs by chemical type and therapeutic significance), which was in effect at the time the 1984 Amendments were under consideration in Congress. FDA's longstanding interpretation of the term "new molecular entity" is that it is a compound containing an entirely new active moiety. FDA's interpretation of the scope of the 5-year exclusivity provision is also consistent with the legislative history, which reveals that Congress was aware of FDA's classification scheme and did not intend to confer significant periods of exclusivity on minor variations of previously approved chemical compounds. (*See*, *e.g.*, Cong. Rec. H9124 (September 6, 1984) (statement of Representative Waxman); H. Rept. 857, Part I, 98th Cong., 2d Sess. 38 (1984).).

54 Fed. Reg. 28872 (July 10, 1989). When FDA issued the final rule in 1994, it explained its interpretation in light of the *Abbott* decision:

> Although the court of appeals appeared to agree with the agency's conclusion that exclusivity should be limited to the first approved product containing the active moiety, the court found the agency's parsing of the operative statutory phrase "active ingredient (including any salt or ester of the active ingredient)" to be linguistically impermissible as set forth in the agency's administrative decision denying 10-year exclusivity to Abbott. Rather than interpret the term "active ingredient" broadly to include the concept of active moiety, the agency interpreted the term narrowly to refer to the form of the moiety in the product, but interpreted the parenthetical phrase "(including any salt or ester of the active ingredient)" broadly to include all active ingredients that are different but contain the same active moiety. Although the court noted that the agency had, subsequent to the administrative decision, voiced the more linguistically permissible construction (interpreting the term "active ingredient" to refer to active moiety), the court found that it could not consider this construction because it was not relied upon in the administrative decision.

59 Fed. Reg. 50338, 50358 (Oct. 3, 1994). FDA went on to conclude that "active ingredient," as used in the phrase "active ingredient (including any salt or ester of the active ingredient)," means "active moiety," as defined in 21 C.F.R. § 314.108.

The district court in *Actavis Elizabeth LLC v. FDA*, 689 F. Supp. 2d, 174 (D.D.C. 2010), held that the term "active ingredient (including any ester or salt of the active ingredient)" is ambiguous under *Chevron* step one. *Id.* at 178. That court noted, "Congress did not define 'active ingredient' in the statute," and that "the Court of Appeals for the District of Columbia Circuit already has concluded that the statutory language 'no active ingredient (including any ester or salt of the active ingredient) of which has been approved in any other application' is ambiguous." *Id.* (citing *Abbott Labs. v. Young*, 920 F.2d 984, 987 (D.C. Cir. 1990)). In affirming judgment in favor of FDA, the D.C. Circuit appears to have accepted the district court's *Chevron* step one conclusion without stating so explicitly. *See Actavis Elizabeth LLC v. FDA*, 625 F.3d 760, 764-65 (D.C. Cir. 2010) ("Since nothing in the text, structure, purpose, or legislative history of the statute speaks directly to the precise question at issue, the agency's interpretation must stand if it is reasonable.") (internal quotation and citation omitted).

Of Counsel:

WILLIAM B. SCHULTZ
General Counsel

ELIZABETH H. DICKINSON
Associate General Counsel,
Food and Drug Division

ANNAMARIE KEMPIC
Deputy Chief Counsel, Litigation

SHOSHANA HUTCHINSON
Associate Chief Counsel, Litigation
U.S. Department of HHS
Office of the General Counsel
10903 New Hampshire Avenue
White Oak 31 Room 4560
Silver Spring, MD 20993-0002

Respectfully submitted,

BENJAMIN C. MIZER
Acting Assistant Attorney General

MICHAEL S. BLUME
Director

/s/ *Ann F. Entwistle*

ANN F. ENTWISTLE
Trial Attorney
Consumer Protection Branch
Civil Division
U.S. Department of Justice
P.O. Box 386
Washington, DC 20044
202-305-3630
ann.f.entwistle@usdoj.gov

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