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June 11, 2007

By Facsimile [301-796-9877]
and First-Class Mail

Thomas Abrams, RPh, MBA
Director
Division of Drug Marketing, Advertising, and Communications
10903 New Hampshire Ave.
Bldg 22 Rm 1400
Silver Spring, MD 20993-0002

Re: NDA # 50-724
Abelcet® (Amphotericin B Lipid Complex Injection)
MACMIS # 15020

Dear Mr. Abrams:

On May 21, 2007, the Division of Drug Marketing, Advertising, and Communications (DDMAC) sent a warning letter to Enzon Pharmaceuticals, Inc. (Enzon) alleging that a flashcard (ABL 100-059-0806) for Abelcet® (Amphotericin B Lipid Complex Injection) was misleading and therefore misbranded the drug in violation of section 502(a) of the FDCA, 21 U.S.C. § 352(a). For the reasons discussed below, we respectfully request that DDMAC withdraw the letter.[1]

Unsubstantiated Allegations of Misleadingness

DDMAC interprets certain statements in the flashcard as claims of superiority or efficacy but fails to support its interpretations with market research or data from studies designed to assess the messages that the intended audience takes away from the flashcard.

For example, DDMAC objects to certain statements in the flashcard regarding the mortality consequences of treating with antifungal therapy more than 48 hours after the first positive blood

[1] In previous correspondence with you, we have listed all of the previous letters in which we explained our objections to DDMAC's efforts to regulate the content of prescription drug communications. For the sake of brevity, we are discontinuing that practice. All of the concerns WLF is raising in this letter to you have been raised before.

sample. DDMAC contends that, "in conjunction with" claims elsewhere in the flashcard regarding the pharmacokinetic difference between Abelcet and AmBisome, these statements "create a claimed . . . survival advantage[] for Abelcet when no such advantage has ever been shown."

It is not at all clear that DDMAC's interpretation of these statements is defensible. It seems entirely proper for Enzon to point to the importance of timely initiation of appropriate treatment for invasive fungal infections. Indeed, DDMAC concedes—albeit grudgingly—that "early initiation of treatment with an effective drug for a life-threatening illness may indeed be prudent." DDMAC also acknowledges that the flashcard "accurately depict[s]" the results of the study by Morrell *et al*., which demonstrated that patients who were treated early had a lower risk of mortality than patients treated later. DDMAC's attribution of a superiority claim to the flashcard is particularly troubling given that the statements regarding the benefits of early treatment *do not mention Abelcet*—as DDMAC concedes.

DDMAC also fails to provide support for its conclusion that the flashcard implied that "early initiation of Abelcet reduces hospital mortality" and that Abelcet is "clinically superior to AmBisome in reducing mortality from invasive fungal infections," as it contends. In fact, it is not clear that anyone other than the DDMAC personnel involved in the preparation and review of the letter would believe that the flashcard's presentation of *in vitro* data implied these or any other claims of clinical efficacy, especially in light of Enzon's disclaimer to the contrary ("Results from *in vitro* data do not necessarily predict clinical efficacy.").

DDMAC interprets the tagline, "Right Choice. Right Now." by itself as a claim that Abelcet is better than any other treatment option. An equally plausible interpretation is that Abelcet is an effective drug for the treatment of invasive fungal infections and that timely initiation of therapy is an important determinant of clinical outcomes. Both contentions would be amply supported.

Impermissible Approach to the Dissemination of Scientific Information

Even if the flashcard did contain clinical efficacy claims based solely on *in vitro* data, Enzon would be entitled to include such claims in its promotional materials. Despite DDMAC's assertion that "*in vitro* data do not constitute substantial evidence to support a claim or implication of superior clinical effectiveness" (apparently based on 21 C.F.R. § 202.1(e)(6)(vii)), FDA itself has recognized the clinical relevance of *in vitro* data. In fact, FDA's prescription drug labeling regulations provide for the presentation of *in vitro* data in dosing-related sections. *Id*. § 201.57(c)(3)(iv), (c)(11). Furthermore, applications for the approval of new drugs require the inclusion of data from *in vitro* studies conducted by the manufacturer. *See id*. § 314.50. DDMAC's attempt to preclude Enzon from using *in vitro* data in support of its claims is to that extent inconsistent with FDA's own regulatory requirements.

At a minimum, DDMAC must permit the presentation of *in vitro* data with disclaimers as necessary to assure that the presentation is truthful and non-misleading. To the extent that any statement about data from a study is potentially misleading, the First Amendment entitles the manufacturer to use, and requires DDMAC to accept, disclaimers sufficient to ensure that the statement is truthful and non-misleading. *See Pearson v. Shalala*, 164 F.3d 650, 657-58 (D.C.

Cir. 1999), *reh'g denied*, 172 F.3d 72 (D.C. Cir. 1999) (FDA may not simply ban claims that are not supported by "significant scientific agreement," but must instead consider whether the disclaimers will make the claims not misleading). DDMAC's uncorroborated conclusion that Enzon's disclaimer ("Results from *in vitro* data do not necessarily predict clinical efficacy.") is not sufficient to address any potential of the flashcard to mislead therefore infringes on Enzon's First Amendment right to disseminate information by not allowing the use of disclaimers to ensure that a statement is non-misleading.

No Authority to Seek Corrective Advertising

Finally, DDMAC does not have the statutory authority to request that Enzon disseminate "corrective" messaging. The FDCA does not include the authority to request "corrective" messages as one of the agency's enforcement tools. 21 U.S.C. § 331 *et seq*. We have previously advised DDMAC that its requests for corrective messages are unauthorized, unconstitutional, and imprudent, but we have received no response. We object to DDMAC's continuing policy of requesting that pharmaceutical companies engage in "corrective" messaging without pointing to the statutory basis for these requests. We again request that you address our concerns in writing.

Conclusion and Requested Action

We request that DDMAC immediately withdraw the warning letter to Enzon concerning Abelcet. We urge DDMAC to cease the issuance of warning and untitled letters and advisory correspondence that contain allegations the same as or similar to those described above.

The deficiencies described in this letter do not necessarily constitute an exhaustive list. DDMAC must ensure that its actions with respect to prescription drug promotion, and to other forms of commercial speech, comply with the First Amendment, and do not exceed FDA's statutory authority under the FDCA.

Sincerely,

Richard A. Samp
Chief Counsel

cc: Sheldon Bradshaw (GCF-1)