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

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

Re: NDA # 20-989
Evoxac Capsules (cevimeline hydrochloride)
MACMIS ID # 14792

Dear Mr. Abrams:

On January 12, 2007, the Division of Drug Marketing, Advertising, and Communications (DDMAC) sent a warning letter to Daiichi Sankyo, Inc. (DSI) alleging that a wall calendar (DSEV-6-0028) and dry-erase board (DESV06-0029) for Evoxac Capsules (cevimeline hydrochloride) "misbrand" the drug "in violation of" sections 502(a) and 201(n) of the Federal Food, Drug, and Cosmetic Act (FDCA), 21 U.S.C. §§ 352(a) and 321(n). For the reasons discussed below, WLF requests that DDMAC withdraw the warning letter. WLF requests, further, that DDMAC initiate a comprehensive review of its policies and procedures to assure that they comply with the First Amendment and do not exceed FDA's authority under the FDCA.[1]

Problematic Policy of Requiring Double Disclosure of Risk Information

DDMAC contends that the wall calendar and dry-erase board "de facto" omit risk information because the risk information included in each piece would not be visible "or even accessible" when the pieces are "adhered to walls or similar surfaces."

[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.

WLF believes that DDMAC's objection is legitimate. We do not agree, however, with DDMAC's allegation that, "even if the information on the back . . . could be accessed . . . , the misbranding would not be cured." DDMAC asserts that section 502(a) requires the inclusion of risk information "in the same place in which the effectiveness claims appear" and is not satisfied by presenting risk information "in another part of the materials."

DDMAC relies on 21 C.F.R. § 202.1(e)(3) to support the theory that risk information must appear twice in prescription drug promotional materials. But this regulation states that qualifying information may appear concisely in each part of an advertisement if accompanied by a reference to more complete qualifying information elsewhere in the piece:

> If any part or theme of the advertisement would make the advertisement false or misleading by reason of the omission of appropriate qualification or pertinent information, that part or theme shall include the appropriate qualification or pertinent information, which *may be concise if it is supplemented by a prominent reference on each page to the presence and location elsewhere in the advertisement of a more complete discussion of such qualification or information*.

DDMAC has effectively read that important qualifier out of the regulation. Nowhere does DDMAC's letter acknowledge that FDA's own regulations contemplate advertisements that do not present risk information verbatim in two separate places. If § 202.1(e)(3)(i) meant that all risk information must appear in the creative part of the advertisement, then every advertisement would presumably have to include all the risk information appearing in the package insert both in the creative part of the advertisement and in the brief summary part of the advertisement. This would be an absurd result, and is clearly not contemplated by the regulation.

Moreover, such a view would raise grave constitutional questions. The First Amendment requires the government to justify requiring manufacturers to disclose risk information in the creative part of an advertisement when this information already appears in the accompanying brief summary. *See Pearson v. Shalala*, 164 F.3d at 659 ("[A]ll the government offers in support is the FDA's pronouncement that 'consumers would be considerably confused' . . . . [T]he government . . . must still meet its burden of justifying a restriction on speech—here the FDA's conclusory assertion falls far short.") (citations and footnote omitted). Given that the complete risk information sections of the package insert ordinarily appear in the brief summary, it seems highly doubtful that such justification could be provided.

Even if this position were tenable in substance, it would be invalid for procedural reasons. At one time, FDA's view was that promotional communications for prescription drugs had only to refer the reader to the location of complete risk information, which could appear on a separate page. *See* 50 Fed. Reg. 36,677 (1985) ("[T]he brief summary is intended to ensure a 'fair balance' between a drug's potential benefits and risks in all prescription drug advertisements."). As of 1996, the agency's position had changed. *See* 61 Fed. Reg. 48,708 (1996) (FDA "traditionally" has required risk information in the body of the advertisement). FDA's failure to use notice-and-comment rulemaking or to provide a reasoned analysis justifying this change of position renders its current stance invalid. *See Motor Vehicle Mfrs. Ass'n v. State Farm Mut.*

Auto. Ins. Co., 463 U.S. 29, 42 (1983); *Alaska Prof. Hunters Ass'n, Inc. v. Federal Aviation Admin*., 177 F.3d 1030, 1033-34 (D.C. Cir. 1999).

The "double-disclosure" theory advanced in DDMAC warning and untitled letters presents important policy questions. FDA has recognized repeatedly that disclosing too much risk information in promotional material can cause "information overload," precluding comprehension and/or distracting attention from the most important facts. Most recently, in finalizing new regulations intended to make package inserts easier for practitioners to use by, among other things, focusing the risk-information sections on scientifically substantiated risks, FDA stated that "labeling that includes theoretical hazards not well-grounded in scientific evidence can cause meaningful risk information to lose its significance . . . . Overwarning, just like underwarning, can . . . have a negative effect on patient safety and public health." *See* Requirements on Content and Format of Labeling for Human Prescription Drug and Biological Products, 71 Fed. Reg. 3,922, 3,935 (Jan. 24, 2006).

Consistent with this sensible position, FDA has also taken steps to evaluate effective risk communication in patient-directed materials. In 2004, in a draft guidance document intended to improve patient comprehension of risk information in print advertisements by reducing the volume and improving the format of that information, CBER and CDER stated: "In general, FDA believes that exhaustive lists of minor risks distract from and make it difficult to comprehend and retain information on the more important risks." *See* CBER & CDER, Guidance for Industry: Brief Summary: Disclosing Risk Information in Consumer-Directed Print Advertisements (DRAFT) (Jan. 2004). The double-disclosure theory is irreconcilable with FDA's "less is more" theory of risk communication and is therefore invalid. *Harco Holdings v. United States*, 977 F.2d 1027, 1035-36 (7th Cir. 1992) (agency position "is not only new and unsupported by agency practice or rulings, . . . [but also] internally inconsistent" and therefore "deserves no deference").

Conclusion and Requested Action

For the reasons discussed above, we request that DDMAC immediately withdraw the warning letter to DSI and cease the issuance of warning and untitled letters and advisory correspondence that contains allegations the same as or similar to those described above. We request that you review, in a systematic fashion, all of your policies and procedures to ensure that they provide sufficient room for sponsors to disseminate, and health care practitioners and patents to receive, truthful and non-misleading information about prescription drugs. We request, further, that you respond to the numerous legal and policy issues we have raised in our correspondence with you since 2005.

The deficiencies described in this letter do not necessarily constitute an exhaustive list. It is DDMAC's responsibility to ensure that its actions comply with the First Amendment, and do not exceed FDA's statutory authority.

Sincerely,

Richard A. Samp

Chief Counsel

cc: Sheldon Bradshaw (GCF-1)