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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 # 20-762
Nasonex® (mometasone furoate monohydrate) Nasal Spray, 50 mcg
MACMIS # 14548

NDA # 20-121
Flonase® (fluticasone propionate) Nasal Spray, 50 mcg
MACMIS # 13807

Dear Mr. Abrams:

On May 7, 2007, the Division of Drug Marketing, Advertising, and Communications (DDMAC) sent untitled letters to Schering Corporation (Schering) and GlaxoSmithKline (GSK) alleging that professional detail aids for Nasonex (mometasone furoate monohydrate) Nasal Spray, 50 mcg and Flonase (fluticasone propionate) Nasal Spray, 50 mcg, respectively, "misbrand[ed] the drug[s] 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, DDMAC should withdraw the letters.[1]

Questionable Allocation of Limited Agency Resources

[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 questions the advisability of devoting resources to these two untitled letters. Although DDMAC has not issued a formal statement of its review priorities, the most recent description of which we are aware states that DDMAC considers "the overall impact on public health, whether the drug in question is new or has a high-risk profile, and whether the drug has a history of problems." Staff of the Sen. Comm. on Finance, Use of Educational Grants by Pharmaceutical Manufacturers 6 (Apr. 2007) (available at http://www.finance.senate.gov/press/Bpress/prb042507a.pdf). DDMAC's letters do not—and could not, because of the well-established and highly favorable safety profile of intranasal corticosteroids—allege any safety concerns associated with the two visual aids. FDA's Index to Drug-Specific Information (http://www.fda.gov/cder/drug/drugsafety/DrugIndex.htm), which provides the latest risk information about drugs with emerging safety issues, contains no reference to either Nasonex or Flonase. It is therefore hard to see how sending these untitled letters is consistent with DDMAC's own expressly identified priorities.

Nor can we understand how the untitled letters protect or promote the public health. The *gravamen* of DDMAC's complaint is that Schering and GSK have each claimed that its own product was superior to its competitors without adequate substantiation. The letters do not focus on any patient safety issue. Indeed, the lone reference to patient safety (on page 2 of the GSK letter) does no more than suggest a relationship between use of Flonase in patients under age 4 and a potential "reduction in growth velocity"—a relationship that is far from substantiated, as the approved labeling for the drug acknowledges. This purely hypothetical issue is not sufficient to justify DDMAC's devotion of the substantial resources necessary to generate these two letters. This is particularly the case given alternative means available for competitors to resolve disputes such as this one. *See* Lanham Act § 43(a), 15 U.S.C. § 1125(a).

It appears, from the nature of the allegations and the issuance of the letters on the same day, that DDMAC has become embroiled in a competitive dispute between two manufacturers of intranasal corticosteroids. Although FDA has statutory and regulatory authority to take action with respect to any false or misleading statement in promotional labeling, DDMAC has repeatedly taken the position that it is so resource-constrained that it cannot execute the most basic components of its mission without an infusion of additional resources. *See User Fee Deal for Ad Review Stems from PhRMA DTC Principles*, THE PINK SHEET, Dec. 4, 2006, at 4. It is therefore ill-advised for DDMAC to have squandered staff time on what is essentially a competitive dispute having little or no relationship to the public health.

We urge DDMAC to refrain from using its limited resources to adjudicate competitive disputes that raise insubstantial public health issues. Instead, DDMAC should devote those resources to providing guidance in the myriad areas in which it is sorely needed.

Unsubstantiated Allegations of Misleadingness

DDMAC alleges that the detail aids for Nasonex and Flonase contain a variety of implied claims. For example, DDMAC alleges that the detail aid for Nasonex implies that patients prefer Nasonex to Flonase "based on all of the attributes assessed in the 'preference study' and that patients prefer Nasonex to Flonase overall . . . ." DDMAC's allegations are unsupported by data from studies designed to assess the messages that health care practitioners take away from the detail aid. DDMAC's continued insistence on interpreting promotional materials without the

benefit of objective corroboration raises important statutory and constitutional issues. This issue is fully addressed in our previous submissions.

DDMAC's interpretations of statements in the visual aids present another important issue: the interpretations appear deliberately calculated to be more expansive than could possibly be supported by the manufacturers' cited substantiations. For example, according to the Schering letter, the visual aid for Nasonex implies that patients prefer Nasonex to Flonase "overall." DDMAC alleges that this implied claim of "overall" patient preference cannot be substantiated by data from the study cited by Schering to support the statements in the visual aid. This is bound to be the case, because the cited study was designed to substantiate a narrower preference claim relating to specific sensory attributes such as scent and aftertaste. According to DDMAC: "Patient preference encompasses multiple aspects of patient experiences such as convenience, ease of use, dosing, dosage form, all aspects of efficacy, and adverse events."

DDMAC fails to acknowledge that the visual aid *does not contain an unqualified claim of "overall" patient preference.* Rather, it states that patients preferred Nasonex "[b]ased on scent and taste attributes"—specifically, scent/odor, immediate taste, and aftertaste. Moreover, the visual aid carefully explains that the patient preference claims are based on data from a multicenter, double-blind, crossover, clinical preference study of 100 subjects who assessed the products according to 8 sensory attributes: scent/odor, immediate taste, aftertaste, less drip down, less run out, soothing, less irritation, and urge to sneeze. The visual aid states prominently that surveyed subjects preferred Nasonex 2:1 with respect to three of the sensory attributes, and further made clear that the study only included "scent and taste attributes."

Using this technique of attributing meaning to selected statements far beyond what could fairly be inferred from the statements, and without regard for either the specific language used by a manufacturer or the nature of the substantiating data, DDMAC is able effectively to ban any statement in a promotional piece to which it objects. As we have previously explained, the First Amendment requires DDMAC to have data corroborating its interpretations of promotional pieces and prohibits DDMAC from banning promotional claims that are based on sources of information that do not meet the unreasonably high "substantial evidence" standard (discussed below). The untitled letters to Schering and GSK further illustrate the perilous consequences of DDMAC's current policies and procedures, which acknowledge no constitutional limitation.

Inappropriate Treatment of Comparative Claims

DDMAC's allegation that the detail aid for Flonase contains unsubstantiated superiority claims highlights the agency's firmly established policy of allowing drug manufacturers to make promotional claims regarding products only if those claims are supported by "substantial evidence." According to DDMAC, the reference cited by GSK "does not provide substantial evidence" because the "study design raises multiplicity issues" and the "study was not replicated." DDMAC's position, that promotional claims may only rely for substantiation on sources that meet FDA's high standard—the same standard used to determine whether a drug is approvable—not only harms the public health by keeping new scientific developments from health care practitioners, but also raises significant questions under the First Amendment. As a legal matter, a prescription drug manufacturer is entitled to make statements in its promotional

materials based on sources of information that do not meet federal regulators' definition of an adequate and well-controlled clinical investigation.

It is a bedrock of First Amendment law that the government may not ban speech based on its potential to mislead, if the speech is presented in a manner that is truthful and non-misleading. The most obvious way for DDMAC to comply with this principle would be to allow sponsors to make promotional claims based on clinical investigations and on other sources of data and information as long as those claims are presented with any necessary disclaimers. *Central Hudson Gas & Elec. Corp. v. Public Serv. Comm'n*, 447 U.S. 557, 565 (1980) ("The State cannot regulate speech that poses no danger to the asserted state interest, nor can it completely suppress information when narrower restrictions on expression would serve its interest as well."); *Bates v. State Bar*, 433 U.S. 350, 375 (1977) ("the preferred remedy is more disclosure, rather than less"). Consistent with these constitutional principles, DDMAC must allow manufacturers to convey information about their products to health care practitioners—even if that information is (in DDMAC's view) obtained from clinical studies that do not meet DDMAC's exacting standards.

In this instance, GSK and Schering are entitled to make truthful and non-misleading statements in their promotional materials, regardless of whether FDA is aware of the supporting data, or considers the data to be sufficiently "substantial." FDA is not a peer-review mechanism for the medical community. *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 67 (D.D.C. 1998). Because scientific viewpoints may differ as to the usefulness of any particular study in clinical practice, the only course that respects First Amendment values is for DDMAC to allow truthful and non-misleading claims about all studies, whether or not they are deemed acceptable by FDA. *West Virginia State Bd. of Educ. v. Barnette*, 319 U.S. 624, 642 (1943). DDMAC's approach of precluding GSK from make comparative claims based on data of which FDA is not aware or does not find sufficiently "substantial" would deprive physicians of useful information about therapeutic products in violation of the First Amendment. *Virginia State Bd. v. Virginia Citizens Consumer Council*, 425 U.S. 748, 757 (1976) (The Court has not "recognized any . . . limitation on the independent right of the listener to receive the information sought to be communicated."); *Roe v. Ingraham*, 364 F. Supp. 536, 543 (S.D.N.Y. 1973) ("the First Amendment has been held to include a correlative right to receive information and ideas"). To the extent that any claims may be misleading, under the First Amendment, manufacturers are entitled to use, and DDMAC is required to accept, disclaimers sufficient to ensure that the statements are truthful and non-misleading. *See Pearson v. Shalala*, 164 F.3d 650 (D.C. Cir.), *reh'g denied*, 172 F.3d 72 (D.C. Cir. 1999).

We have previously objected to DDMAC's issuance of warning and untitled letters stating that companies may not use clinical investigations or other sources of information in promotional materials unless DDMAC has determined that these sources are satisfactory. DDMAC clearly has an established practice and policy of banning any statements, even if truthful and non-misleading, that are based on clinical investigations that DDMAC deems inadequate. For the reasons discussed above, we renew our objection.

Untenable Allegations of Broadened Indication/Overstatement of Efficacy

DDMAC alleges that the detail aids for Nasonex and Flonase imply that the products are effective in the treatment of the specific symptom of nasal congestion when this has not been demonstrated by substantial evidence. This allegation cannot be supported. First, the detail aids are peppered with references to allergies. Moreover, the detail aids were disseminated with copies of the FDA-approved labeling, which contains the complete labeled indication for the products. Under the circumstances, it is hard to see how a physician could possibly interpret the detail aids as making unqualified claims of efficacy in treating "congestion."

Second, because "congestion" is not a distinct disease state but rather a symptom of, among other things, allergies, it is not at all clear that anyone other than the DDMAC personnel involved in the preparation of these letters would have thought that the products were indicated for congestion alone. We are not aware of any lawfully marketed drug products that are marketed for the relief of nasal congestion without also identifying an underlying disease state. Indeed, FDA's OTC drug monograph for nasal decongestant drug products requires manufacturers to state in labeling that their products are indicated for the treatment of nasal congestion *caused by* cold, allergic rhinitis, or sinusitis. *See* 21 C.F.R. § 341.80(b)(1).

DDMAC also alleges that statements relating to the congestion component of a composite nasal symptom score overstate the efficacy of Nasonex and Flonase in the absence of data demonstrating that the products are effective in treating nasal congestion. This allegation is untenable. Both detail aids contain detailed information regarding the relationship of the congestion component symptom to the composite endpoint. For example, the detail aid for Flonase explains that Total Nasal Symptom Score (TNSS) "is the sum of individual scores for each of the symptoms evaluated by patients," including nasal congestion, runny nose, sneezing, and nasal itching. Moreover, the detail aid for Flonase refers to congestion specifically in the context of seasonal allergic rhinitis—the header for the relevant page encourages physicians to "Choose greater efficacy for your patients with *seasonal allergic rhinitis"* (emphasis added), and the same page states in the lower right-hand corner that Flonase should be prescribed "when nasal congestion is certain but the triggers are not," *i.e.*, when the *allergen* is unidentified but seasonal allergic rhinitis is the cause of nasal congestion.

In sum, the detail aids disclose more than enough information about the studies upon which the companies rely for the claims not to be misleading. DDMAC's allegations make clear that FDA has an established policy of not allowing companies to employ disclaimers to address any potential of a statement to mislead, despite the First Amendment requirement that the government refrain from imposing a blanket ban on potentially misleading speech when any such potential can be obviated through use of disclaimers.

Problematic Policy of Requiring Double Disclosure of Risk and Other Information

Finally, DDMAC asserts that the detail aid for Flonase is misleading because it "fails to present the full approved indication." DDMAC's objection ignores the fact that the detail aid was disseminated with copies of the FDA-approved labeling—which contained the "full approved indication"—and that each page of the detail aid directed recipients to the labeling. Health care practitioners thus had ready access to the very information that DDMAC alleges was omitted, and that information was presented in precisely the manner dictated by FDA. Moreover,

DDMAC does not present any evidence that health care practitioners reading the detail aid were misled by the manner in which the indication was presented.

DDMAC's position that prescription drug manufacturers must present risk and other information not only in the FDA-approved labeling that accompanies the promotional communication, but also in the "creative" part of the labeling piece itself, is both legally vulnerable and inconsistent with broader FDA policies. We have described these deficiencies repeatedly and in detail in previous correspondence with you, and in our citizen petition.

Conclusion and Requested Action

We request that DDMAC immediately withdraw the untitled letters to Schering and GSK concerning Nasonex and Flonase, respectively. 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)