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March 4, 2003

S. Mitchell Weitzman
Center for Drug Evaluation and Research
HFD-7
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Andrx Citizen Petition FDA Docket No. 02P-0493/CP 1

Dear Mr. Weitzman:

In this letter, Procter & Gamble ("P&G") and AstraZeneca, LP ("AstraZeneca") respond to the Citizen Petition filed November 21, 2002 on behalf of Andrx Pharmaceutical Corp., FDA Docket No. 02P-0493/CP 1 ("Andrx Citizen Petition"). P&G and AstraZeneca are seeking approval for the OTC marketing of Prilosec1 for the prevention of frequent heartburn -- heartburn occurring two or more days a week (NDA 21-229). In its Citizen Petition, Andrx requests that FDA deny the application, on the grounds that "P&G/AstraZeneca have not demonstrated that Prilosec1 can be used safely and effectively by consumers who purchase the drug OTC" for the prevention of frequent heartburn. *See* Andrx Citizen Petition at 1-2.

As set forth in more detail below, Andrx's contentions are baseless. The Prilosec1 NDA has been fully supported by data from the sponsors and has undergone significant review by the agency, including consideration by two joint sessions of the Nonprescription Drugs Advisory Committee and the Gastrointestinal Advisory Committee (the "Advisory Committee"). The latest session of the Advisory Committee heard testimony from the NDA sponsors, FDA representatives, and interested members of the public (including Dr. Robert Niecestro of Andrx Laboratories), and engaged in extensive discussion of all the issues raised before it. *See* FDA Transcript of Joint Public Meeting of the Nonprescription Drugs Advisory Committee and the Gastrointestinal Advisory Committee (June 21, 2002) ("Advisory Committee Transcript").

At the conclusion of its proceedings, the Advisory Committee voted 16 to 2 that pending modifications to product labeling, confirmed by a label comprehension study, Prilosec1 was safe and effective for the OTC indication sought. The Andrx Citizen Petition -- which revisits many of the issues considered in detail by the Advisory Committee, but adds nothing new -- does not alter the basis for the Advisory Committee's recommendation or for the "approvable" letter issued by the FDA.

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Discussion

In its petition, Andrx begins with the general assertion that "the NDA for Prilosec1 should be denied outright because the sponsors have not met their burden of showing that consumers can use Prilosec1 safely and effectively in an OTC setting." *See* Andrx Citizen Petition at 1, 11-13. As noted above, however, the Advisory Committee voted 16 to 2 that "the sponsor *has provided sufficient information to support the approval*" of Prilosec1 for OTC use, with appropriate modifications to product labeling. *See* Advisory Committee Transcript at 281 (emphasis added).

The Advisory Committee based its conclusions on safety and efficacy data from the clinical studies submitted by P&G/AstraZeneca in their original NDA for Prilosec1,[1] *see id.* at 12-13, 130-144, as well as new studies on label comprehension and actual use submitted in support of the current NDA, *id.* at 144-165. In response to an Action Letter in which FDA indicated that Prilosec1 was "approvable" for OTC use, the sponsors are actively working with the agency to modify the product labeling and conduct the consumer label comprehension study requested by the Advisory Committee and the FDA.

In addition to its very general assertion that P&G/AstraZeneca have not "met their burden," Andrx sets forth five specific grounds on which it contends Prilosec1 is non-approvable.[2] As set forth in the following paragraphs, however, every one of these five issues was reviewed and discussed by the Advisory Committee before it voted in favor of approvability.

The risk of masking more serious diseases. The Advisory Committee gave full consideration to the question whether OTC use of Prilosec1 in a 14-day course could mask the occurrence of more serious diseases in the population treated. *See* Advisory Committee

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[1] On January 27, 2000, the sponsors submitted their original NDA seeking approval of Prilosec1 for OTC use in the treatment and prevention of episodic heartburn. The original application was for a 10 mg dose, while under the current application the dose is 20 mg. *See* Advisory Committee Transcript at 131; FDA Center for Drug Evaluation and Research, OTC Medical Officer's Review for Prilosec1 (April 16, 2002), at 6-7. The Advisory Committee considered the original Prilosec1 NDA on October 20, 2000, and found the product non-approvable for the indications submitted. *See* Advisory Committee Transcript at 131.

[2] These five grounds are set forth in subparagraphs (b) through (f) of Section 2 of the petition. *See* Andrx Citizen Petition at 13-26. In addition, Andrx asserts under subparagraph (g) that if approved, Prilosec1 must be marketed under a different name to avoid confusion with the prescription product. *See id.* at 26-27. Andrx provides no basis for its assertion that consumers are at risk of being misled by the trade name "Prilosec1." Even if such a risk existed, the impact on safety would be minimal, because the 20 mg dose for which OTC approval is now sought is the same as the prescription dose for Prilosec.

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Transcript at 55 (presentation by Dr. Peura for P&G); 77-78 (presentation by Dr. Levine, AstraZeneca); 99-100 (discussion between Dr. Davidoff, Committee Member and Dr. Triebwasser, P&G); 135-37 (presentation by Dr. Avigan, FDA); 238 (comment by Dr. Neill, NDAC Consultant); 265-66 (comment by Dr. Brass, NDAC Consultant); 274-75 (comment by Dr. LaMont, Committee Member); 311-312 (comment by Dr. Davidoff, Committee Member).

As reflected in the outcome of the votes taken at the end of the session, the Advisory Committee did not see a significant risk that consumers' use of Prilosec1 for frequent heartburn would lead them to avoid seeking medical care for underlying ailments. For example, the Advisory Committee voted 12 to 6 that consumers who had a recurrence of heartburn symptoms after a 14-day course of Prilosec1 responded "appropriately," including by seeking the advice of a healthcare professional. *See* Advisory Committee Transcript at 246-250, 255. Several individuals directly expressed the view that patients who do not obtain relief after the 14-day labeled course of treatment are likely to seek the advice of a physician. *See id.* at 222 (comment of Dr. Ganley, FDA); 275-76 (comment by Dr. Cryer, Committee Member).

The Advisory Committee also voted 17 to 1 that "the proposed 14-day duration of therapy" was appropriate for the labeled population. *See id.* at 264, 278. As one committee member stated, "I think 14 days is right because if we are worried about . . . masking other diseases with this treatment, then this would be a good balance between efficacy for a simple symptom and avoidance of masking." *Id.* at 275 (comment of Dr. LaMont, Committee Member).

The effectiveness of the product on day one. At the Advisory Committee meeting, the sponsors presented evidence showing that while heartburn prevention "increases over the first few days of dosing," the effect on heartburn is "both clinically and statistically significant . . . on day one, for day 14 and across all 14 days." *See* Advisory Committee Transcript at 58. The effectiveness of the product on day one was specifically discussed by the Advisory Committee. Dr. Uden (Committee Member) provided the following comment: "I absolutely understand that it starts working the first day." *See id.* at 246.

Andrx's suggestion that OTC approval of Prilosec1 raises a danger of overdose, *see* Andrx Citizen Petition at 20, is without basis. An actual use study submitted by the sponsors demonstrated excellent compliance with the dosing directions for the product: 96% of subjects took no more than one tablet per dose and 91% of subjects took only one tablet per day. *See* Advisory Committee Transcript at 69. In addition, there were only three people out of 758 in the actual use study who took multiple daily doses of the product. None of them exceeded three doses a day and none experienced a serious adverse event. *See id.* at 70-71. This actual use study, which was conducted in an OTC setting, yielded no evidence of individuals taking unsafe quantities of the product because of perceived lack of effectiveness on day one.

Interaction of Prilosec1 with food. In his presentation before the Advisory Committee, Dr. Robert Niecestro of Andrx Laboratories stated that an "FDA-requested definitive drug/food interaction study [on Prilosec1] has either not been done and/or reported," and asked for further information on food interactions. *See* Advisory Committee Transcript at 21-22.

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Shortly thereafter, however, an FDA representative indicated that "the sponsor has submitted as part of their NDA . . . a food effects study to evaluate the effect of food on the pharmacokinetics of omeprazole and magnesium tablets and there is significant food effect. We are probably going to recommend it be administered an hour before meals." *See id.* at 25. Drug/food interaction was the subject of further discussion before the committee, *see id.* at 94-95 (discussion between Dr. Lamont, Committee Member and Dr. Triebwasser, P&G), as well as a further presentation by the sponsors, *see id.* at 195-98. P&G/AstraZeneca believe that sufficient information has been submitted to FDA on food/drug interactions, and that this is reflected in the Advisory Committee's 16-2 vote in favor of approvability.

Interaction of Prilosec1 with other drugs. Andrx contends that inadequate consideration has been given to "the risks associated with the use of contraindicated medications *other than* anti-heartburn medications in conjunction with OTC Prilosec." *See* Andrx Citizen Petition at 22 (emphasis in original). In fact, the Advisory Committee heard detailed presentations on the potential interaction of Prilosec1 with a variety of drugs including warfarin, phenytoin, diazepam, and digoxin. *See* Advisory Committee Transcript at 134-35 (presentation of Dr. Avigan, FDA); 188-195 (presentation by Dr. Levine, AstraZeneca and Dr. Triebwasser, P&G); *see also id.* at 59, 61-2, 66-7 (presentation by Dr. Bierer, P&G on drug interaction issues in context of label comprehension and actual use studies), 22-25 (presentation of Dr. Niecestro, Andrx Laboratories on interaction with other heartburn medications). The potential risks posed by interactions with these drugs and others including clarithromycin, ketoconazole, and itraconazole, as well as the appropriate methods for addressing those risks in the product labeling, were further explored in discussions throughout the Advisory Committee meeting. *See id.* at 165-69 (discussion between Dr. Brass, NDAC Consultant, Dr. Alfano, NDAC Industry Liaison Representative, and FDA representatives Dr. Shetty and Dr. Lechter); 171-74 (discussion between Dr. Johnson, Committee Member; Dr. Cantilena, Committee Chair; Dr. Alfano, NDAC Industry Liaison Representative; sponsor representatives Dr. Peura and Dr. Zorich; and FDA representative Dr. Houn); 198-206 (discussion between Dr. Brass, NDAC Consultant; Dr. Davidoff, Committee Member; Dr. Cantilena, Committee Chair; Dr. Triebwasser, P&G; and FDA representatives Dr. Ganley and Dr. Houn).

In his presentation on behalf of the FDA, Dr. Avigan stated: "The potential for critical omeprazole-induced increases in circulating levels of some drugs such as warfarin, phenytoin, diazepam, digoxin *is small but can be further minimized by appropriate consumer labeling*. Similarly, the more likely disruption of effective levels of antifungals such as ketoconazole *can be minimized by labeled instructions to consumers*." *See id.* at 135 (emphasis added). Near the conclusion of the session, several members gave specific suggestions as to how drug-drug interactions might be handled in the product labeling. *See id.* at 286 (comment of Dr. Lam, Committee Member), 300-01 (comment of Dr. Brass, NDAC Consultant), 304 (comment of Dr. Cryer, Committee Member). The sponsors of the Prilosec1 NDA are working with the agency to craft appropriate labeling on drug-drug interactions.

Risks associated with use by particular subpopulations. The Advisory Committee heard testimony on the effects of proton pump inhibitors (PPIs) in certain ethnic subpopulations, such as Asian populations. *See* Advisory Committee Transcript at 34-35 (presentations by Dr.

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Wolfe, Chair of the Advisory Board for Gastrointestinal Drugs, appearing as an interested member of the public). Ethnic subpopulations were included in the sponsors' safety data, and FDA has concluded that "there is no evidence that common side effects are predisposed to occur in particular racial groups." *See* FDA Division of Gastrointestinal and Coagulation Drug Products, Medical Officer's Review for OTC Prilosec (January 27, 2000), at 3. While the Asian subpopulation are "slower metabolizers" of omeprazole, there is no evidence that omeprazole accumulates with repeated dosing. In addition, the approved prescription labeling for Prilosec in Japan does not make any changes in the dosing recommendations, even for this population.

At the conclusion of its session, the Advisory Committee was charged to vote on five issues relating to the approvability of Prilosec1 for OTC use in the prevention of frequent heartburn. *See* Advisory Committee Transcript at 210-212. On four out of five of these votes, including the final vote on approvability, the result was strongly positive in favor of approving Prilosec1 for the OTC indication sought.[3]

On the one negative vote out of five, the Advisory Committee voted 15 to 3 that the sponsor had not yet demonstrated that consumers with heartburn could adequately self-select when using Prilosec1 in the OTC setting. *See id.* at 234-35. Even on this vote, subsequent discussion by committee members indicates that many concerns about improper self-selection can be resolved through modifications to the product labeling. *See id.* at 240 (comments of Dr. Uden and Dr. Williams, Committee Members), 243-44 (comments of Dr. Alfano, NDAC Industry Liaison Representative and Dr. Goldstein, Industry Liaison Representative); *see also id.* at 225 (comment of Dr. Neill, NDAC Consultant that "I don't think we're talking about safety and efficacy today. We did that two years ago. I think we're talking about patient selection for this indication and labeling and label comprehension for this indication."). In addition, there is some question as to whether even those members who voted in the negative perceive a significant self-selection problem with Prilosec1. *See id.* at 238 (comment of Dr. Neill, NDAC Consultant that "of those that selected inappropriately, the majority of those seemed to be patients who had heartburn less than once per week and simply are taking a very effective medicine for their not as severe condition . . . While I voted no, that they can't self-select, it doesn't seem to matter much"), 243 (comment of Dr. Johnson, Committee Member that "I agree with Dr. Neill and others that those who selected incorrectly is probably clinically irrelevant").

Conclusion

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[3] Specifically, the Advisory Committee voted (1) 16 to 2 that it was acceptable to have some patients with GERD plus or minus erosive esophagitis self-treat with OTC medication, *see* Advisory Committee Transcript at 230, 231; (2) 12 to 6 that consumers who had a recurrence of heartburn symptoms after taking Prilosec1 responded appropriately, for example by seeking the advice of a healthcare professional, *see id.* at 246, 250, 255; (3) 17 to 1 that the proposed 14-day duration of therapy was acceptable for the labeled population, *see id.* at 264, 278; and (4) 16 to 2 in favor of approvability, *see id.* at 281.

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As demonstrated above, every issue raised in the Andrx Citizen Petition has already been reviewed and discussed by the Advisory Committee, which voted 16 to 2 that with appropriate labeling modifications, Prilosec1 is approvable for OTC use in the prevention of frequent heartburn. Consistent with the conditions set forth in the FDA "approvable" letter, the sponsors are working with the agency to craft appropriate labeling and to perform the recommended label comprehension study. As the Andrx Citizen Petition provides no new information relevant to the Prilosec1 review process and the sponsors are working with FDA to revise the product labeling, the Andrx Citizen Petition should be denied in its entirety.

Sincerely,

Paul A. Franz