ZUCKERMAN SPAEDER LLP

1201 CONNECTICUT AVENUE, NW WASHINGTON, DC 20036-2638
202 778 1800 202 822 8106 fax www.zuckerman.com

0744 '03 JUN 12 P2:04

CARLOS T. ANGULO
(202)778-1811
CTANGULO@ZUCKERMAN.COM

June 12, 2003

VIA HAND DELIVERY

Dockets Management Branch
Food and Drug Administration
Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket Number 02P-0493/CP 1 (Andrx Citizen Petition)

Dear Sir or Madam:

This letter responds to the March 4, 2003 letter from Proctor & Gamble and AstraZeneca, LP ("March 4 Letter") urging FDA's denial of Andrx Pharmaceutical Co.'s November 20, 2002 Citizen Petition ("Andrx Petition"). The Andrx Petition opposed approval of an over-the-counter version of Proctor & Gamble/AstraZeneca's Omeprazole Magnesium product (brand-name Prilosec1) (hereafter "OTC Prilosec1").

The Andrx Petition opposed OTC Prilosec1 on the general grounds that Proctor & Gamble and AstraZeneca had not shown that their product would be safe and effective if used in an OTC setting. More specifically, Andrx contended that the sponsors had not conducted adequate clinical trials to determine the risks of using OTC Prilosec1 in an OTC setting and had not developed adequate labeling to apprise consumers of those risks. The Petition identified several specific issues on which the sponsors' testing and the product's labeling were inadequate.

The March 4 Letter responded to the Andrx Petition by arguing that all the issues raised in the Petition had been addressed and resolved at a June 21, 2002 joint session of the FDA's Nonprescription Drugs and Gastrointestinal Advisory Committees (hereafter "Advisory Committee"), and that, pending some additional revisions to the product label, nothing stands in the way of FDA's approval of OTC Prilosec1.[1]

[1/] As noted in a May 29, 2003 letter to S. Mitchell Weitzman of FDA, Andrx was not copied on the March 4 letter.

02P-0493 RC 1

The March 4 letter in no way militates against FDA's granting of the Andrx Petition. In their letter, Proctor & Gamble and AstraZeneca have overlooked the many concerns FDA has expressed regarding OTC Prilosec1. They have also misconstrued the import of the Advisory Committee's determination on June 21, 2002 that OTC Prilosec1 is "approvable." FDA should grant the Andrx Petition and deny approval to OTC Prilosec1. At a minimum, the Agency should follow its Advisory Committee's recommendation and require Proctor & Gamble and AstraZeneca to substantially revise the OTC Prilosec1 label and to conduct additional label comprehension studies. Once those studies have been completed, the Agency should resubmit the product's label and the new studies to the Advisory Committee *and the public* for consideration in an open forum, so that the Committee and the public can evaluate whether the many flaws in the sponsors' previous proposed label for OTC Prilosec1 have been cured and make recommendations to the Agency.

1. The March 4 Letter Ignores FDA's Many Serious Concerns About OTC Prilosec1

The fact that the Advisory Committee tentatively deemed OTC Prilosec1 to be "approvable" does not resolve the many concerns expressed by FDA itself, as well as by Advisory Committee members, about that product. The Agency is not bound by the Advisory Committee's determination of approvability, and, in fact, FDA's findings with respect to OTC Prilosec1 actually compel a determination that that product cannot presently be approved, and may not be able to be approved at all

In its Petition, Andrx catalogued FDA's many findings regarding the propriety of an OTC version of Prilosec. These findings and FDA's discussion of these findings during the Advisory Committee review process cast into significant doubt whether consumers could use OTC Prilosec1 safely and effectively. In the course of its review of OTC Prilosec1, FDA found that:

- OTC Prilosec1 did not provide immediate relief from heartburn on Day 1 of use, although it grew in effectiveness over the course of the 14-day dosing regime.

- Even at the end of the 14-day dosing regime, approximately 30 percent of the participants in the actual use study experienced an episode of heartburn despite using the OTC medication according to directions, and approximately 40 percent of subjects with high frequency heartburn experienced such episodes.

- Of those individuals who suffered a recurrence of heartburn after completing the 14-day treatment regimen, only 20 percent consulted their physicians, despite instructions on the proposed OTC label to do so.

- Many consumers who suffered from infrequent heartburn inappropriately self-selected OTC Prilosec1.

- Consumers were likely to select OTC Prilosec1 for episodic relief, not just for prevention of heartburn, and therefore would use the drug in an ineffective and improper manner.

- Many consumers (37 percent of actual use participants) failed to follow the dosing directions set forth on the proposed OTC label (1 tablet per day for 14 days).

- Consumers were likely to take OTC Prilosec1 in conjunction with other anti-heartburn medication and other contraindicated medications, despite warnings on the proposed OTC label not to do so or to consult a physician before doing so.

- Consumers with contraindicated symptoms took OTC Prilosec1, despite label warnings cautioning against such use.

- Consumers who were unlikely to follow up with a physician if their heartburn symptoms returned after the conclusion of a 14-day dosing regime might instead "simply choose to continue treatment chronically if symptomatic relief is afforded." FDA determined that this course of conduct raised significant safety concerns, in light of the possibility that long-term usage would "'mas[k]' symptoms associated with underlying medical conditions that warrant early diagnosis and adequate treatment," including cancer of the esophagus or stomach.

- As a general matter, rates of proper self-selection were lower for low-literacy and non-Caucasian consumers. In fact, label comprehension among some low-literacy groups ranged around only 50%.[2]

Many of FDA's concerns date back to the first Agency review of an OTC version of Prilosec in 2000 and have gone unaddressed ever since by Proctor and Gamble and AstraZeneca. FDA's findings demonstrate that consumers cannot safely and effectively use OTC Prilosec1. As discussed in the Andrx Petition, the Agency's determinations show not only that the labeling for OTC Prilosec1 is inadequate, but also that the sponsors have not conducted sufficient clinical studies to evaluate the risks associated with use of Prilosec – risks that include the masking of more serious diseases, adverse drug-food and drug-drug interactions, and overdosing.

[2/] *See* Andrx Petition at pp. 6-9 and accompanying notes.

The assertions by Proctor & Gamble and AstraZeneca in the March 4 Letter that all these issues were conclusively resolved at the Advisory Committee meeting are simply untrue and ignore the very real, unresolved concerns expressed by FDA and Advisory Committee members on these issues.

By way of example, the March 4 Letter suggests that the Advisory Committee rejected the notion that the repeated use of OTC Prilosec1 could mask serious diseases. Proctor & Gamble and AstraZeneca, however, ignore the fact that FDA itself, as well as members of the Advisory Committee, has repeatedly expressed its concerns about masking and has also criticized the sponsors' failure to address this issue. *See, e.g., OTC Medical Officer's Review for Prilosec1*, April 16, 2002 (cited on page 5 of the Andrx Petition), at 30 (noting that methodology of sponsor's actual use study "does not allow [FDA] to address concerns [about repeated uses]"); *Advisory Committee Transcript* (cited on page 6 of the Andrx Petition) at 227 (Comments of Advisory Committee Member Dr. Louis Cantilena) (noting that "[consumers of OTC Prilosec1] will probably recurrently treat themselves inadequately possibly' and that "the consequences of that . . . hasn't [sic] been studied obviously"). There is nothing in the Advisory Committee Transcript to suggest that either FDA or the Advisory Committee no longer regarded masking as a serious problem in connection with OTC Prilosec1.

Also by way of example, the March 4 Letter suggests that OTC Prilosec1 has been shown to be effective on the first day of treatment and that the Andrx Petition's concerns about the consequences of this initial lack of effect are misplaced. This is false. The data in fact shows clearly that OTC Prilosec1 provided full relief from heartburn on Day One in less than 50 percent of tested subjects. *See Advisory Committee Transcript* at 103 (Comments of Dr. Michael Camilleri citing sponsor data). Indeed, Dr. Donald Uden, the very same Advisory Committee quoted in the March 4 Letter for the proposition that OTC Prilosec1 works on Day One, specifically criticized the sponsors' proposed labeling because it lacked "any statement that you will not see this medication work for one or two days." *Advisory Committee Transcript* at 180. The March 4 Letter is simply an effort to paper over the very real concerns addressed by FDA and Advisory Committee Members and the sponsors' own failure to address these concerns through both clinical studies and labeling improvements.

In sum, FDA's own findings, as well as the sponsors' responses to those findings, compel the conclusion that OTC Prilosec1 is not ready for approval, notwithstanding the Advisory Committee's determination that that product is in some abstract way "approvable" if certain conditions are met.

2. The March 4 Letter Misconstrues the Import of the Advisory Committee's Vote on "Approvability"

Even if the FDA adopts the Advisory Committee's recommendations, it is important to understand the effect and implications of the Advisory Committee's determination that OTC Prilosec1 is "approvable." In short, the minimum possible consequence of the Advisory Committee's vote is that OTC Prilosec1 must be subjected to additional labeling testing and must undergo further review before the Advisory Committee, in an open public forum, before it may be approved by FDA.

The Advisory Committee's vote on approvability must be viewed through the prism of the Committee's threshold determination, by an overwhelming 15-3 vote, that consumers with frequent heartburn could *not* adequately self-select OTC Prilosec1. Indeed, when asked to consider whether OTC Prilosec1 was "approvable," Committee members were instructed to vote "yes" *even if* they determined that there were significant deficiencies in the sponsors' proposed labeling that prevented adequate self-selection and *even if* they believed that additional studies were necessary to determine whether any changes to the labeling proposed by the sponsors were sufficient. *Advisory Committee Transcript of June 21, 2002 Public Meeting* (cited hereafter as "*Advisory Committee Transcript*") at 280. And as the post-vote discussion (*Advisory Committee Transcript* at pp. 281-318) reveals, virtually every Committee member deemed the proposed labeling to be highly deficient and in need of substantial revision and emphasized the need for additional label comprehension studies prior to the marketing of OTC Prilosec1.

In the context of a prescription product, the issue of labeling is of somewhat less importance, since for those products, a patient can rely on the advice of a physician to help the patient interpret and comply with the labeling instructions. In the context of an over-the-counter product, by contrast, labeling is *of paramount importance* because the labeling instructions provide patients with the *only* advice they will receive on how to use the product. It is therefore of the utmost importance that labeling instructions be clear and complete. The Advisory Committee on June 21, 2002 found the proposed labeling for OTC Prilosec1 to fall far short of these goals.

While the post-vote discussion on June 21, 2002 was notable for the uniform dissatisfaction of Advisory Committee Members with the sponsors' proposed labeling, it was equally notable for the breadth of recommendations by Committee Members on how to improve the labeling, and for the lack of consensus among Committee Members on exactly what changes were necessary to make OTC Prilosec1 approvable. A review of the June 21, 2002 Advisory Committee Transcript reveals that virtually every aspect of the proposed labeling came under criticism, and that virtually every Committee Member had different ideas about how to make the labeling acceptable. For example:

- Dr. John Lamont focused on the label's failure to address repeat dosing and urged that the label be revised to indicate that dosing instructions be limited to 2-3 times a year. *Advisory Committee Transcript* at 283-284.

- Dr. Francis Lam recommended that the label limit repeat dosings to twice a year. *Id.* at 286-287

- Dr. Robert Levine recommended that the label be revised to include bold, redlined text regarding "alarm symptoms" and further recommended that "communication techniques, educationally-wise or on the print", be used to notify the consumers about when to contact a physician. Dr. Levine concurred that dosage instructions be limited to 2-3 recurrent episodes. *Id.* at 287.

- Dr. Edwin Gilliam concurred with Dr. Levine on "alert symptoms" and further recommended changes to the label that would address "tips for managing the heartburn" and "lifestyle modification" issues. *Id.* at 288.

- Susan Cohen deemed the labeling "totally inadequate" and indicated the need to give consumers "a lot more . . . education". *Id.* at 289.

- Dr. Richard Neill focused on the need to explain in the labeling how OTC Prilosec1 works differently from other heartburn medications and suggested that any labeling without this explanation was "misleading" to consumers. *Id.* at 290.

- Dr. Leslie Clapp concurred with Dr. Lam on his recommendation that recurrent dosings be limited to twice a year. He also urged that the label "address in a very clearly stated manner that [OTC Prilosec1] is not for acute relief of symptoms" and that "it would be useful to guide consumers as to when to expect maximum relief." *Id.* at 291. Dr. Clapp expressed particular concern for the ability of low literacy population to understand the labeling. *Id.*

- Dr. Nancy Geller stated that she was "very concerned about the label as written", and in particular about the ability of low-literacy population to read and understand the labeling instructions. Dr. Geller made a number of specific recommendations regarding the text of the labeling and urged that the sponsors of OTC Prilosec1 develop benchmarks for use in pre-approval label comprehension studies. Finally, Dr. Geller opposed any limit on recurrent dosages greater than one, in light of the lack of data on the effect of recurrent dosages. *Id.* at 292-293.

- Dr. Donald Uden recommended limiting dosages to two treatments in two months, noting that he was "a little different in that aspect than others." Dr. Uden also recommended that the label expressly state "'[t]he symptoms will last for 24 hours. You may not see symptom relief for six to eight,' or whatever number you want to use that will be supported by literature should be in there as an educational piece." *Id.* at 295.

- Dr. Henry Williams recommended language addressing both the drug-food interaction issue and the issue of delays in onset. *Id.* at 296.

- Dr. Ronald Fogel agreed with the limitation of 2-3 dosages a year, but emphasized the need for language expressly stating that "if symptoms are not better after two courses or if you require more than three courses of the drug in a year you should see a doctor." Dr. Fogel also took issue with the language in the proposed labeling that addressed what to do if the consumer suffered chest pain or wheezing, contending that the language "needs to be made much strong[er]" in that respect. *Id.* at 297.

- Dr. Eric Brass made a number of specific suggestions regarding labeling on the issues of drug-drug interactions, pregnancy warnings, and the need for "more appropriate bolding and coloring and highlighting for the more significant messages." He also expressed skepticism on the issue of repeat dosage instructions, supporting the concept in principle but noting that "this is a relatively abstract concept at the time of purchase to communicate to a consumer." *Id.* at 299-303.

- Dr. Julie Johnson emphasized that there were "a lot of changes needed." She identified a number of different statements on the proposed label that needed clarification or improvement, addressed the importance of using brand names when discussing drug-drug interactions, and emphasized the need to strengthen the message that the product was for prevention and not relief of episodic use. *Id.* at 304-307.

- Dr. Louis Cantilena, the Advisory Committee Chairman, indicated that the label "needs a lot of help and revision" and was "in great need." Dr. Cantilena also emphasized that "approval of [OTC Prilosec1] would be significant new ground for the Agency." *Id.* at 308-309.

The foregoing summary clearly reveals three things: first, that virtually every Committee member strongly believed that the OTC Prilosec1 label was in need of substantial revision; second, that the Committee, as a whole, identified virtually every problem noted in the Andrx Petition as a reason for denying approval of the product; and third, that there was no consensus among Committee members on what changes were needed to make the label adequate.

Under the circumstances, it is plain that the Advisory Committee's vote does not amount to an endorsement of OTC Prilosec1, nor did the Committee provide sufficient guidance to FDA on the question of what labeling changes were necessary to make that product approvable. To the contrary, the Committee's discussion reveals that its dissatisfaction with the proposed label stemmed in part from the fact the sponsors of OTC Prilosec1 had not conducted sufficient studies to determine the risks caused by the use of their product, and therefore had not developed, and could not develop, an appropriate response to those risks through labeling.

Even if the Committee's final determination could be read to preclude the need for additional clinical studies on Prilosec1, it cannot be read to foreclose additional label testing and subsequent Committee and public review of the product labeling. Indeed, at a minimum, the Committee's final determination on OTC Prilosec1 requires that labeling changes be implemented, that these changes be subjected to label comprehension and actual use studies, *and that these changes and studies be resubmitted to the Advisory Committee and the public for review and comment in an open forum.* The Advisory Committee has deemed OTC Prilosec1's proposed labeling to be far short of adequate and has made a wide range of (sometimes conflicting) recommendations on how to make the labeling adequate. The Committee must be given another chance to review the labeling and to assess the tests supporting the labeling changes, to determine whether the changes made by Proctor & Gamble and AstraZeneca meet the Committee's standards, and to subject the sponsors and FDA to questioning on the proposed changes. The public too should be given an opportunity to weigh in on these changes, just as it has had an opportunity to participate in the review process at every step of the way thus far. FDA has indicated that one of the principal purposes of the Advisory Committee review process "serves an important function by providing a public forum for discussion of issues." 50 Fed. Reg. 7452 (February 22, 1985). The June 21, 2002 public meeting did not resolve the issue of OTC Prilosec1's label (except to confirm that the labeling as proposed was inadequate) and it would disserve the public function of the Advisory Committee process to permit FDA to resolve this issue behind closed doors.

As noted above, the issue of labeling is absolutely critical in the OTC context. Given the many problems with the sponsors' proposed labeling for OTC Prilosec1, it would disserve the public health for FDA, at a minimum, to permit the marketing of that product without the seal of approval of the Advisory Committee and the public on the version of labeling that consumers will have to read and follow. Only through such additional review can FDA be certain that the labeling changes comply with the mandates issued by the Advisory Committee last June, and that these changes are

subjected to public scrutiny before the OTC Prilosec1 is brought to market. And only through these steps can the transparency and public dialogue that is the goal of the Advisory Committee process be achieved.

Respectfully submitted,

Carlos T. Angulo

Carlos T. Angulo
Counsel for Andrx Pharmaceutical Co.

cc: S. Mitchell Weitzman
Paul A. Franz