MEMORANDUM

Department Of Health and Human Services
Food and Drugs Administration
Center For Drug Evaluation and Research
Division of Over-the-Counter Drug Products (HFD-560)

Date: June 20, 2003

From: Charles J. Ganley, M.D. _____
Director, Division of Over-the-Counter Drug Products (HFD-560)

Subject: Andrx Citizen Petition regarding Prilosec OTC (NDA 21-229)

To: Jonca Bull, M.D.
Director, Office of Drug Evaluation V

Florence Houn, M.D.
Director, Office of Drug Evaluation III

We are aware of a Citizen Petition dated November 21, 2002, submitted on behalf of Andrx Pharmaceutical Corp., requesting that FDA deny the approval of the Proctor and Gamble's (the sponsor's) application to market Prilosec (omeprazole) over-the-counter (OTC).

The petition itself identifies three major points and then proceeds to identify a number of specific issues. These three points are addressed first followed by a response to the specific grounds articulated in the petition.

A supplement to their petition dated June 12, 2003 requests that the agency submit the studies completed since the meeting of the Joint Nonprescription & Gastrointestinal Drugs Advisory Committees (Joint Advisory Committee) on June 21, 2002 to another advisory committee session, in an open public forum, before approval action is taken. This point is listed as the fourth major point.

I. The Petition's Major Points (Petition at 1)

1. The sponsor's NDA should be denied because they have not met their burden of showing that consumers can use Prilosec OTC safely and effectively in an OTC setting.

Based on FDA's review of the sponsor's application, we believe that they have met their burden of showing that consumers can use Prilosec OTC safely and effectively in an OTC setting. The sponsor submitted two adequately controlled studies to demonstrate efficacy and safety (Study 171 and 183) for a population of frequent heartburn sufferers.[1] The sponsor has also conducted five actual use studies and five label comprehension studies in order to assess the risks associated with OTC use of the product and establish how best to ensure its safe and effective use by consumers. In the most recent review cycle, the sponsor submitted Study 22103. This label comprehension study provided sufficient information to

[1] Dr. Justice Division Director memo dated June 19, 2003

respond to the deficiencies described in the August 8, 2002 approvable letter.[2] FDA has reviewed these studies and concluded that the application should be approved because Prilosec OTC is safe and effective for its intended use.[3]

The petitioner has not provided any new data or new information to support their concerns. All of the issues raised by the petitioner were raised in FDA reviews of the sponsor's data or during FDA advisory committee meetings[4] to discuss the OTC availability of Prilosec, and have been satisfactorily resolved. The petitioner's interpretation of the data is inconsistent with the interpretation of the data of the majority of the experts at the June 21, 2002 Advisory Committee. At the conclusion of its proceedings, the Joint Advisory Committee voted 16 to 2 that pending modifications to the product labeling, confirmed by a label comprehension study, Prilosec OTC was safe and effective for OTC use. Based on the merits of the data, we concurred with the recommendations of the advisory committee and concluded that Prilosec OTC is safe and effective for OTC use.[5]

2. Even if OTC Prilosec could be used safely and effectively in an OTC setting, the sponsor has not conducted sufficient studies to assess the risks associated with OTC use of the product or to establish how best to ensure its safe and effective use by consumers.

As noted above, the sponsor has completed five actual use studies and five label comprehension studies in order to assess the risks associated with OTC use of the product and establish how best to ensure its safe and effective use by consumers. The development of drugs for OTC marketing is an iterative process often depending on multiple consumer behavior studies such as actual use and label comprehension studies. The petitioner suggests that an actual use study[6] is warranted to address remaining issues but has not described why the information needed must be obtained from an actual use study as opposed to a label comprehension study. The advisory committee identified the consumer behavior issues that required further study and recommended a labeling comprehension study as the mechanism to obtain the information.[7] We agreed with their recommendation. As discussed above, the final label comprehension study provided sufficient information to address our concerns described in the August 8, 2002 approvable letter and for us to conclude that Prilosec OTC is safe and effective for OTC use.[8]

3. Even if no additional studies are necessary, Prilosec OTC should not be approved until the sponsor makes significant changes to the product label, including but not limited to those changes recommended by the Joint Advisory Committee.

Significant changes have been made to the label, as summarized in my review dated June 20, 2003. The sponsor conducted a label comprehension study that evaluated consumer comprehension of the Use, Warnings and Directions sections of the label. Based on the review of this study,[9] we believe that the sponsor has provided adequate information to support the OTC marketing of Prilosec OTC.

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[2] Dr. Ganley Division Director memo dated June 20, 2003

[3] Dr. Chin review dated October 17, 2000; Dr. Lechter reviews dated May 23, 2002, and May 2, 2003; Dr. Shetty reviews dated October 25, 2000, May 10, 2002, and April 25, 2003

[4] October 20, 2000 and June 21, 2002.

[5] Dr. Ganley Division Director memo dated June 20, 2003.

[6] The petition has used the term "clinical Study" instead of "actual use Study", although "actual use Study" more accurately represents the requests made in the petition.

[7] June 21, 2002 Advisory Committee transcripts

[8] Dr. Ganley Division Director memo dated June 20, 2003

[9] Dr. Shetty April 23, 2003 review and Dr. Lechter May 2, 2003 review

4. The agency should submit the studies completed since the meeting of the Joint Nonprescription & Gastrointestinal Drugs Advisory Committees (Joint Advisory Committee) on June 21, 2002 to another advisory committee session, in an open public forum, before approval action is taken.

The question of whether to consult an advisory committee regarding issues involved in our review of human prescription drug products is committed solely to FDA's discretion as described in 21 CFR 14.171. We reviewed the single study submitted by the sponsor of the application since the June 21, 2002 advisory committee meeting and believe it is a well-conducted study. This study, in addition to the previous information submitted to the application, provides sufficient information to support the approval of Prilosec OTC. There are no remaining issues that warrant further discussion before an advisory committee. After deliberations were completed at the June 21, 2002 advisory committee meeting, the committee noted they did not need to reconsider the issues raised unless we felt there to be a need.[10]

II. Specific Statement of Grounds

1. The petitioner asserts that while prescription Prilosec has been shown to be safe and effective for *symptomatic* heartburn associated with GERD, the sponsor have not demonstrated that consumers can use Prilosec OTC safely and effectively for the different purpose of *frequent* heartburn (Petition at 2). Additionally, the petitioner asserts that even if Prilosec OTC could be used safely and effectively by consumers in an OTC context for the prevention of heartburn, the sponsor have not demonstrated that conditions for safe and effective use are present. To do so, the petitioner maintains, the sponsor must (1) study the unsupervised use of the drug and identify the risks likely to result from such use, and (2) develop adequate labeling that will apprise consumers of these risks. The sponsor has done neither, the petitioners argue, “despite the abundant evidence that consumers will not use OTC Prilosec in the manner directed by the manufacturer and that such misuse can cause Prilosec 1 to be used in an unsafe and ineffective manner” (Petition at 2,3).

Heartburn is accepted by the agency to be a symptom that consumers can identify and self treat in the OTC setting.[11] In the past, the OTC indications for heartburn medicines have been limited to acute symptom relief and prevention of meal or beverage induced heartburn. The indication for Prilosec is a new indication for a population of frequent heartburn sufferers (occurring two or more days per week). The sponsor has conducted two efficacy/safety studies and numerous consumer behavior studies (actual use and label comprehension) to support the safety and efficacy of OTC omeprazole. The safety and effectiveness of OTC omeprazole has been scrutinized at two different FDA Advisory Committee meetings, and FDA has conducted numerous reviews of these studies. After reviewing the data in the most recent amendment to their NDA, we believe the sponsor has provided sufficient information to support the safe and effective OTC marketing of omeprazole for frequent heartburn.[12]

The petitioner has requested that the sponsor "study the unsupervised use of the drug and identify the risks likely to result from such use". The sponsor has done just that with Study 007[13], which was discussed by the Advisory Committee on June 21, 2002. This study was the primary study for the committee to review. Based on this study, the advisory committee voted overwhelmingly to support the approval of OTC Prilosec.[14] In the course of their deliberations, they recommended that additional testing be conducted to address some of the deficiencies in consumer behavior identified by Study 007. The

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[10] June 21, 2002 advisory committee transcripts at 318

[11] 21 CFR 331

[12] Dr. Ganley Division Director memo dated June 20, 2003.

[13] Dr. Shetty review dated April 16, 2002

[14] The committee voted 16 for and 2 against approval of the application. (June 21, 2002 Advisory committee transcripts at 231.)

committee recommended a label comprehension study, rather than an actual use study, to evaluate pending labeling issues. We agreed with their recommendation. The sponsor conducted Study 22103, which we have concluded supports the approval of the application.[15] By successfully conducting this study, the second part of the petitioner's request, "develop adequate labeling that will apprise consumers of these risks", has been achieved. Based on the results of Study 22103, we believe the sponsor has developed adequate labeling that will apprise the consumer of important risks.

2. The petitioner asserts that the sponsor has not demonstrated that consumers are able to self-select and de-select appropriately and that those who do self-select will use OTC Prilosec safely and effectively (e.g., following label use directions for duration of use and knowing when seek advice from a healthcare provider (Petition at 11).

The petitioner fails to note that the development of OTC drug products is an iterative process. Label comprehension and actual use studies often identify situations where consumers may not understand how to appropriately use the product. The sponsor has conducted five actual use and five label comprehension studies during the development of this product. Most of the concerns associated with the petitioner's statement are based on the outcomes of the earlier studies, which helped to identify the areas that required further study.

For the final phase in the development of this product, the sponsor conducted Study 22103. This was one of the largest label comprehension studies that we have asked a sponsor to conduct. It evaluated three different labels and assessed the comprehension in literate and low literate consumers with frequent or infrequent heartburn. We have accepted the results of this study as supportive of the final label.[16] As discussed above, this final study provided sufficient information to respond to all outstanding labeling deficiencies and for us to conclude that Prilosec OTC is safe and effective for OTC use.

3. The use of Prilosec 1 in an OTC setting creates the potential for masking serious diseases and for delays in the treatment of these diseases – the sponsor must conduct actual use studies to assess the extent of extended self-medication and potential masking problems (Petition at 13-16). The petitioner provides the following evidence:

   - Evidence presented before the Joint Advisory Committee indicated that (1) the effectiveness of Prilosec 1 for heartburn prevention increased over time, making it likely that consumers could continue to take the drug for recurrent heartburn after the end of the 14-day course of treatment to prevent heartburn; (2) consumers did not follow labeling instructions on how to take the drug and when to consult a physician; and (3) consumers in fact did not see a physician if their heartburn returned after 14 days – despite label warnings that recurring symptoms could be a sign of a serious condition.

   - Data presented to the Joint Advisory Committee revealed 49 cases of stomach cancer in patients taking Prilosec 1, four of which may have been masked by Prilosec 1 therapy. (Petition at 14).

During the development program, we had concerns regarding the masking of more serious conditions. The following points taken collectively address the resolution of this issue:

? During the June 21, 2002 advisory committee meeting, the committee voted on two questions relevant to this issue. First, with regard to the actual use Study 007, the committee was asked " Did consumers who had a reoccurrence of heartburn symptoms respond appropriately?" The committee voted 12 yes

[15] Dr. Ganley Division Director memo dated June 20, 2003

[16] Dr. Ganley Division Director memo dated June 20, 2003

and 6 no. Even though study subjects did not always follow the instructions on the label, the committee felt they often took appropriate alternative actions. Second, the committee was asked "…is the proposed 14 day duration of therapy acceptable for this population?" The committee voted 17 yes to 1 no. We have adopted a 14 day course of therapy as the recommended regimen.

? The short-term use of this product is not a concern in masking symptoms. The product is labeled appropriately to alert consumers about appropriate use. The serious conditions that are cause for concern include erosive esophagitis, Barrett's esophagus and esophageal cancer. Prilosec is an appropriate treatment for erosive esophagitis and Barrett's esophagus. Esophageal cancer is relatively rare and is the least likely to occur of the three. This issue was discussed extensively at the June 21, 2002 advisory committee and they did not believe it to be a major concern. We agree.

? This concern of masking more serious disease is not only applicable to this product but to other OTC heartburn products and other categories of OTC products. For these products, we believe this concern has been adequately addressed by labeling. For example, other acid reducers (e.g., H2 antagonists) are labeled for use for not more than 2 weeks, and internal analgesics (e.g. acetaminophen, nonsteroidal anti-inflammatory drugs) are labeled for use for not more than 10 days.

? The labeling and packaging for Prilosec OTC includes the following to encourage correct use[17]:
  - ? 14 tablet package configurations to encourage use for a 14-day course;
  - ? instructions that limit the repetitive use and the number of courses to be used per year;[18] (These instructions were added to the label as a result of the final label comprehension study.)
  - ? Warnings that alert consumers about other symptoms that may be a sign of a more serious condition.[19]
    (These were also added to the label as a result of the final label comprehension study.)

? Study 22103 evaluated the comprehension of the Use, Warning and Directions sections of a new label and found the comprehension to be high.[20]

4. The petitioner asserts that Prilosec OTC is ineffective for preventing heartburn at the initiation (”Day One”) of treatment, creating the potential for unsafe and ineffective uses of the drug in an OTC setting. The petitioner maintains that the sponsor must conduct additional studies to examine the issue of interaction of Prilosec OTC with other acid reducers, develop labeling that communicates the risks of drug/drug interactions, and conduct studies on the reasons for overdosing **(**Petition at 16-20). Specifically, the petitioner states that:

   - Prilosec has not been proven effective in preventing heartburn during the first 24 hours and only achieves maximum effect after several days, potentially causing consumers to take other anti-heartburn medications at the same time, to an uncertain effect, or to take excessive doses.

   - Evidence suggests that misuse did occur during actual use trials (Petition at 17) while no studies have been conducted on the reasons, extent, and risks of overdosing (Petition at 20).

The petitioner has incorrectly stated the results of the efficacy data. The sponsor conducted Studies 171 and 183, which show that 20 mg of omeprazole showed a significant treatment effect during

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[17] Dr. Ganley Division Director memo dated June 20, 2003.

[18] "Directions" section of the final labeling

[19] "Do not use" and "Ask a doctor before use" if you have sections of the final labeling

[20] Dr. Shetty April 23, 2003 review and Dr. Lechter May 2, 2003 review

the first day.[21] Approximately 50% of the subjects receiving 20 mg omeprazole compared with approximately 30% of placebo subjects had no heartburn during the first day. So, in fact, some people get complete relief of symptoms on the first day. The percentage of persons experiencing complete relief in the omeprazole group continued to increase on subsequent days.

The sponsor did conduct an additional study and tested the concept that complete relief may not occur on the first day. In Study 22103 the sponsor tested whether consumers would understand that some might not achieve a full effect of the therapy on the first day. Approximately 91% of study participants tested on this concept understood it.[22] The labeling of the product reflects the results from this study. The sponsor has made changes to the labeling to reflect that it may take 1 - 4 days for a full effect to occur.[23]

The petitioner has raised questions about the concomitant use of other heartburn medications with Prilosec OTC. This may be particularly relevant when someone first initiates therapy with Prilosec and the maximum benefit has not been realized. We considered what should be said in the labeling and determined that the label should remain silent. This determination is based on the following information, which demonstrates that we do not have sufficient data at this point to support labeling limitations on the use of these drugs: (1) Current prescription labeling permits the concomitant use with antacids, and pharmacokinetic data, as noted by the petitioner, gives conflicting results about an interaction; and (2) There is little clinical information about the interaction of an H2 blocker and a proton pump inhibitor. In addition, if there were an interaction, it would most likely be decreased efficacy (we have no data to suggest a safety issue). The consequence of decreased efficacy is that the product would not provide a benefit and the consumer would not purchase it again. If symptoms recur and they follow labeled instructions, they would then seek the advice of a doctor. Finally, it is unreasonable to expect them to conduct additional studies because this issue is also applicable to other prescription proton pump inhibitors.

5. The petitioner asserts that drug/food interactions, which have generally been found to hinder the effectiveness of Prilosec, have not been sufficiently studied to permit use of the drug in an OTC setting (Petition at 21). The petitioner surmises that this will lead to misuse of the product.

The sponsor has conducted a food effect study. Based on the FDA review of this information[24], there does appear to be a food effect. The final labeling of Prilosec OTC addresses this by instructing consumers to take before eating in the morning. These instructions were similar to the instructions used in one of the clinical efficacy studies that support the indication.

The likelihood of misuse (e.g. taking more than the recommended amount) is more likely to occur in the prescription setting than in the OTC setting because of safeguards incorporated into packaging and labeling of the OTC product:

- The labeling states "do not take more than one tablet a day".
- The OTC product is packaged as 14-day courses of therapy. This is more likely to limit the excessive use of the OTC product compared to a prescription product that may be dispensed in amounts sufficient to supply 1 - 3 months of therapy.
- Study 22103 tested whether subjects knew when to take the product. Comprehension for this concept was close to 90%.[25] Even low literate subjects (~ 80 - 85% comprehension) did quite well in understanding this concept.

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[21] Dr. Justice Division Director memo dated June 19, 2003.

[22] From table 20 - 21 of Dr. Shetty's review dated April 23, 2003.

[23] The sponsor tested language stating "(b)(4)----------. In the efficacy studies, the increase in response appears to plateau at day 4. The final labeling reflects this finding.

[24] Biopharm Review Dr. Al-Fayoumi dated November 13, 2000

[25] From table 20 - 21 of Dr. Shetty's review dated April 23, 2003

6. The petitioner states that the sponsor have not adequately explained the risks associated with the use of contraindicated medications other than anti-heartburn medications in conjunction with Prilosec 1, nor have they adequately justified their decision as to as to which drug/drug interactions to note on the OTC Prilosec label. The petitioner asserts that the sponsor must (1) conduct studies evaluating the drug-drug interactions associated with OTC Prilosec, comparing the relative severity of these interactions with one another; and (2) provide FDA with a clear and compelling reason for the inclusion or exclusion of any particular contraindicated medicine on the product label (Petition at 22-25). Specifically, the petitioner:

   ? States that while the proposed label for OTC Prilosec alerts consumers that they should see a physician before using the drug if they are taking warfarin, phenytonin, or ketoconaxole, the proposed label is likely to be ineffective in steering people away from OTC Prilosec when taking these drugs (Petition at 23-24).

   ? Asserts that even if the labeling on contraindicated medicines were adequate with respect to warfarin, phenytonin, or ketoconazole, the sponsor failed to list other drugs, suggested in prescription Prilosec, that interact in a clinically significant manner with omeprazole (e.g., drugs needed for the proper absorption of gastric acid).

The OTC labeling rule[26] requires that information on drug interactions be incorporated into the **Ask a doctor or pharmacist before use if you are** section of the labeling. Because this information will be in the same location on all labels, this will allow consumers to locate and identify drugs with relative contraindications for use with the product. There are many currently marketed OTC drug products that include possible drug interactions. As the Drug Facts labels become widely available, we expect comprehension of potential interactions with other drugs to improve. The petitioner cites the results from a label comprehension study that suggests frequent heartburn sufferers using medications listed on the label self selected correctly 50% of the time.[27] It is important to note that this improved to 82 % when a list of brand names was given. This result is consistent with the results of a labeling comprehension study suggesting > 80% comprehension on scenarios related to concomitant use of medications.[28] In lieu of including numerous brand names in the Drug Facts labeling, (we would never be able to include them all), we required a brief descriptor on the label for each drug listed. We did not believe additional testing was needed for this concept.

The final Prilosec label lists warfarin, antifungal medicines, diazepam and digoxin in the **Ask a doctor or pharmacist before use if you are** section of the Drug Facts label. We met with the sponsor on January 30, 2001 and decided that these drugs should be included on the label based on possible risks to the consumer.[29] At that time clarithromycin was also considered for the list but later discounted because it causes elevations in omeprazole levels and does not impact on clarithromycin levels. We did not believe that elevated levels of omeprazole related to this interaction with clarithromycin was of significant clinical concern. Although the interaction with digoxin and warfarin is minimal, we decided to include them because of the narrow therapeutic index for both drugs.

7. The petitioner states that the sponsor have not adequately evaluated the risks associated with the use of Prilosec OTC by certain sub-populations (such as those of Asian origin), and have not developed product labeling to warn these sub-populations of these risks (Petition at 25)

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[26] 21 CFR 201.66

[27] June 21, 2002 advisory committee transcripts at 147

[28] June 3, 1998 review of Dr. Lechter and Dr. Aiken (include in Dr. Lechter review of August 16, 2000), Original Study 1

[29] Meeting minutes of January 30, 2001 meeting between FDA and Proctor and Gamble

The petitioner has not provided any data to suggest that sub-populations such as Asians experienced increased incidence of adverse events despite the marketing of the product for 14 years in the prescription setting. The hypothesis surmised in the FDA review[30] cited by the petitioner is hypothetical and the possible consequences are more likely to occur in the prescription setting. They refer to comments by Dr. Michael Wolf at the advisory committee who surmises that long term use can lead to increased gastrin and *potentially* (emphasis added) to more serious diseases long term. Any concerns about the long-term use of this product in various sub-populations are more applicable to the prescription use of the product where patients remain on therapy for extended periods of time.

The petitioner suggests that this sponsor be required to conduct studies to further evaluate the long-term effects of omeprazole in these sub-populations. We disagree. This product is recommended for short-term use (14-day course), and based on the data the sponsor has provided, we believe the majority of consumers will follow the labeled instructions and understand the possible risk of misuse.

We do not believe warnings on the label for these sub-populations are necessary because

- the product is limited to a 14-day treatment period,
- there is no data from the prescription safety database to suggest that these populations experience excess risk,
- in the event some sub-populations may accumulate omeprazole in the blood, there is no evidence that this is harmful over a short period of time.

8. The petitioner states that even if the sponsor's application is approved, Prilosec 1 should be renamed to avoid consumer confusion since it is for a different use than prescription Prilosec (Petition at 26)

The name "Prilosec 1" was withdrawn by the sponsor and replaced with the proposed name "Prilosec OTC". The Division of Medical Errors and Technical Support conducted a review of the proposed name "Prilosec OTC" to determine the potential for confusion with approved proprietary and established names as well as pending names and concluded that there are no objections to the use of the proprietary name, Prilosec OTC**.** [31]

[30] Dr. Mark Avigan review dated January 27, 2000
[31] Division of Medical Errors and Technical Support consult by- D. Toyer 10-11-02