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VIA FEDERAL EXPRESS

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061
5630 Fishers Lane
Rockville, MD 20852

RE: Docket Number 2003P-0366

Dear Sir/Madam:

Mylan Pharmaceuticals Inc. ("Mylan") submits this Comment in support of the Citizen Petition filed with the FDA on August 12, 2003, as well as the letter previously submitted by Mylan dated September 12, 2003 regarding Prilosec OTC (omeprazole magnesium). The Petition requested the FDA to amend its approval of the new drug application for Prilosec OTC (hereinafter referred to as "Prilosec OTC") to require that it be sold under a different brand name in order to eliminate consumer confusion and misuse. Recently, Mylan has obtained new information which necessitates the need for the FDA to take **immediate** action on the Petition. The requested action is important for both regulatory and public health reasons because absent action, Prilosec OTC is being illegally marketed, and such marketing is causing consumers to be **intentionally** misinformed.

Prilosec OTC is **neither** bioequivalent nor therapeutically equivalent to prescription Prilosec. In addition, the OTC product was approved for a single indication and a regimen very different from the prescription product. Despite these significant differences, interchangeability of the OTC product for Prilosec Rx is being assumed and negligently acted upon by all segments of our health care sector, which necessitates urgent correction. The remainder of this Comment provides detail on these issues.

The FDA approved Prilosec OTC in one strength only (20mg), **solely** for the treatment of frequent heartburn occurring two or more days a week, while the prescription version of Prilosec® ("Prilosec Rx") has been approved in three dosage strengths (10mg, 20mg, and 40mg) for not only the treatment of frequent heartburn, but also more serious conditions such as duodenal ulcer, gastric ulcer, gastro-esophageal

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reflux disease (GERD), erosive esophagitis, maintenance of healing of erosive esophagitis and pathological hypersecretory conditions. However, at the time the FDA approved Prilosec OTC, the effect of the approval was unclear with respect to substitution of the over-the-counter version for Prilosec Rx. Recently, the effect has become very clear as Mylan has received information that many Insurers, State Formularies and Physicians are incorrectly assuming that Prilosec OTC is interchangeable for Prilosec Rx regardless of the diagnosis. Additionally, certain State Medicaid programs have mandated that Prilosec OTC be the first line therapy for all proton pump inhibitors. This course of conduct is very dangerous to the safety of the Public in light of the fact that Prilosec OTC is neither therapeutically equivalent or bioequivalent to Prilosec Rx.

In order to demonstrate therapeutic equivalence, drug products must be pharmaceutical equivalents and be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling. Pharmaceutical equivalence is defined as a drug product containing the same active ingredient(s), are of the same dosage form, route of administration and are identical in strength or concentration. (See Preface to the 23rd Edition of the Orange Book) Clearly, Prilosec OTC and Prilosec Rx are not therapeutically equivalent, as the over-the-counter product is a delayed-release tablet formulation containing the magnesium salt of omeprazole, while the prescription product is a delayed-release capsule containing the weak base form of omeprazole. (See Chain Practice Memorandum Attached as **Exhibit A)** Based on the fact that these two dosage forms represent pharmaceutical alternatives, the FDA would not list the two dosage forms as therapeutically equivalent, thus permitting substitution. In addition, Prilosec OTC is not bioequivalent to Prilosec Rx.

Mylan recently conducted a bioequivalency study, which concludes that based on the measurement of the maximum plasma concentration (Cmax), the prescription and the over-the-counter dosage forms are not bioequivalent (the "Study"). (See Study Attached as **Exhibit B**) The Study shows that the Ratio of LN-transformed Cmax of Prilosec OTC relative to Prilosec Rx is 130%. The 90% confidence intervals for the ratio of LN-transformed Cmax for Prilosec OTC relative to Prilosec Rx is 117% - 146%, which is well outside the limits of 80% - 125% prescribed by the FDA for the bioequivalence of two products. This represents a significant difference under the FDA's own standards for bioequivalence. It is highly unlikely that a study could be conducted to demonstrate bioequivalence. (See Declaration by Dr. Marvin C. Myer Attached as **Exhibit C**)

The FDA may have taken into account that Prilosec OTC is not equivalent to Prilosec Rx when weighing the risks and benefits of approving it for the **sole** indication of frequent heartburn, based on **limited** clinical studies of fourteen (14) day administration of 20mg per day of Prilosec OTC. However, in approving Prilosec OTC, the FDA could not have weighed the risk of the **abuse** of Prilosec OTC for treating more severe conditions such as those indicated for Prilosec Rx. One of the underlying assumptions for approving Prilosec OTC is that consumers can properly self-

medicate themselves for up to 3 episodes of heartburn during a year, and will seek physician intervention if they experience more than 3 episodes a year. The clinical studies presented by the sponsors at the June 21, 2002 Advisory Committee Meeting of Nonprescription Drugs and Gastrointestinal were limited to the use of Prilosec OTC for a 14 day regimen up to 3 times a year. Mylan is not aware of any clinical studies which have been conducted to demonstrate the long-term use of Prilosec OTC for more serious conditions which have been studied for Prilosec Rx. (See Physician Desk Reference Book, 12-month clinical studies conducted on Prilosec Rx) In spite of the lack of safety and efficacy data for the long-term use of Prilosec OTC, certain Insurers, State Formularies and Physicians are dangerously assuming that Prilosec OTC can be routinely substituted for Prilosec Rx. Attached are documents prepared and distributed by various segments of our Health Care sector, which demonstrate the need for immediate FDA action. For example, Health Partners states that they are covering an Prilosec OTC because it costs less than $1 per tablet, compared to $3 for generic Prilosec Rx; Priority Health Formulary dictates that consumers "must try and fail Prilosec OTC" and Aciphex before covering Prilosec Rx; North Carolina Medicaid instructs pharmacists to place a **34-days supply** of Prilosec OTC in the days supply field to adjudicate the claim. (See Examples Attached as **Exhibits D, E, & F)**

Furthermore, at the June 21, 2002 Advisory Committee Meeting, the sponsors were questioned on the unintended consequences on the utilization of physicians if insurance and managed care organizations started to pay for over-the-counter omeprazole. Dr. Nora Zorich, V.P. of Pharmaceuticals for Proctor & Gamble responded by stating that "[they] had no indication if [insurers and managed care organizations] will be picking this up, particularly when generics will be on board." (See Advisory Committee Transcript) Unfortunately, the marketing campaign coupled with the economic dynamics of the health care system appear to be dictating that patients who require prescription Prilosec substitute the over-the-counter product because of cost considerations. The benefit of allowing the substitution of Prilosec OTC for Prilosec Rx, with general disregard to the diagnosis, because of cost considerations is grossly outweighed by the potential risks associated with the use of the product for conditions other than frequent heartburn.

The substitution of Prilosec OTC, which has a uniquely different plasma concentration-time profile from Prilosec Rx cannot be assumed to satisfy FDA's safety and efficacy requirements without evidence of clinical studies. In addition, it is clear that the two dosage forms are neither therapeutically equivalent nor bioequivalent, thus presenting safety and efficacy issues. Only those products listed as AB-rated in the Orange Book can be considered for substitution, as such products have demonstrated bioequivalence. Thus, it is very disconcerting that Prilosec OTC is being permitted to be marketed as interchangeable with Prilosec Rx simply because they share the same name. Further, it is imperative that the FDA take immediate action to amend the approval of the

NDA for Prilosec OTC and require that the brand name be changed. Any action short of changing the brand name constitutes false advertising of the product, which leads to further consumer confusion and inevitable misuse because of the intentional lack of credible and complete information.

Sincerely,

Stuart Williams/DDB

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SAW/kaa

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