October 11, 2013

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

CITIZEN PETITION

The Procter & Gamble Company (hereinafter "P&G") submits this Citizen Petition pursuant to 21 C.F.R. § 10.30, and in accordance with 21 C.F.R. Part 314, and 21 U.S.C. §§ 351 and 355.

ACTION REQUESTED

P&G respectfully requests that the Commissioner of Food and Drugs take the following actions:

1. Continue to require similar labeling applicable to all over-the-counter ("OTC") proton pump inhibitors ("PPIs"), substantially equivalent to that approved for Prilosec OTC for subsequent OTC PPIs approved for marketing; this includes:

   (a) Appropriate statements conveying that the product is not intended for immediate treatment of heartburn and instead may take one or more days for full effect, in both the "Use" and "Directions" sections of the Drug Facts Box, such as: "Use . . . not intended for immediate relief of heartburn; this drug may take 1 to 4 days for full effect" and "Directions . . . It may take 1 to 4 days for full effect, although some people get complete relief of symptoms within 24 hours";

   (b) "Directions" that the patient must use the product once a day (every 24 hours), every day for 14 days;

   (c) Statements detailing the appropriate 14-day course of treatment, such as: swallow 1 tablet (capsule) with a glass of water before eating in the morning; take every day for 14 days; do not take more than one tablet (capsule) a day; and do not use for more than 14 days unless directed by your doctor; and

   (d) Appropriate statements conveying that the 14-day course of treatment may be repeated every 4 months, but do not take more than 14 days or more often than every 4 months, unless directed by a doctor.

2. Impose the same rigorous standards upon any pending or future application seeking approval to market a PPI over-the-counter for treatment of frequent heartburn as were imposed during the review of NDA 21-229 for OTC use of Prilosec OTC® (omeprazole 20 mg as omeprazole magnesium 20.6 mg).

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3. If data submitted in support of any pending or future application seeking approval to market an OTC PPI for treatment of frequent heartburn suggests that the label statements referenced in 1.(a) - (d) above could differ from the currently approved statements in the "Use" and "Directions" sections of the Prilosec OTC Drug Facts Box, assure that:

   (a) the differences are clinically significant; and

   (b) the label statements do not explicitly or implicitly convey an impression as to relative safety or efficacy of one OTC PPI over another that lacks adequate substantiation in the form of well-designed comparative studies or that are false or misleading.

STATEMENT OF GROUNDS

I. Background

In contrast to the OTC monograph system where consistency is assured, the serial approval of new drug applications ("NDAs") to market drug products OTC creates the possibility for differences in the approved labeling. These differences can create artificial distinctions between products within the same pharmacological class due to the manner in which the data are presented or considered, resulting in similar products being treated dissimilarly, in contravention of the Administrative Procedure Act. Likewise, it may inadvertently lead to approval of text that conveys false, misleading, or unsubstantiated comparative efficacy claims to consumers who compare label language. This Petition is intended to alert the Commissioner of Food and Drugs to these issues as they impact one class of drugs – PPIs marketed OTC for treatment of frequent heartburn – and request that the Commissioner take appropriate steps to ensure that all such OTC switch applications are subject to the same regulatory standards. In particular, P&G requests that proposed labeling is scrutinized to avoid explicit or implicit implications that an individual PPI has demonstrated superior efficacy over other OTC PPIs at any time, in the absence of data demonstrating that such differences are substantiated.

A. OTC Heartburn Remedies

Heartburn symptoms can vary from person to person, but the primary symptom is a sensation of pain or burning in the chest that begins at the breastbone and moves upward toward the throat, which may be accompanied by a reflux of fluid into the mouth. Reflux of gastric acid into the esophagus is the major cause of heartburn symptoms.

Three classes of compounds are currently available OTC for the relief of heartburn: antacids, H_2-receptor antagonists, and PPIs. Antacids have the longest history of use in the OTC heartburn category. They are regulated under an OTC monograph (*see* 21 C.F.R. Part 331). Antacids work by directly neutralizing existing gastric acid and are indicated "for the relief of heartburn, acid indigestion, and sour stomach." 21 C.F.R. § 331 .30(b). They provide rapid, but relatively short-lived, relief of heartburn symptoms, sometimes necessitating repeat dosing to adequately control heartburn symptoms. Products in this category include Mylanta (aluminum

hydroxide, magnesium hydroxide), Rolaids (calcium carbonate, magnesium hydroxide), Tums (calcium carbonate), and Maalox (aluminum hydroxide, magnesium hydroxide).

H_2-receptor antagonists ("H_2RAs") are systemically absorbed drugs that work by competitively binding to histamine receptors on the surface of the gastric parietal cell, thereby reducing production of gastric acid. The first products in this class were approved for OTC use in 1995. OTC H_2RAs are indicated "for the relief of heartburn, acid indigestion, and sour stomach" and "for prevention of heartburn associated with acid indigestion and sour stomach brought on by certain foods and beverages." These products generally have a relatively rapid onset of action (< 1 hour) and duration of effect of less than 12 hours, and therefore may be dosed up to two times a day. Clinical trials have shown that H_2RAs show diminished effect (pseudotachyphylaxis) with repeat dosing, with a marked decrease in efficacy beginning on the second day; therefore, H_2RAs are not an optimal therapy for frequent heartburn. Products in this category include Zantac (ranitidine HCl), Tagamet HB (cimetidine), Pepcid AC (famotidine), Axid AR (nizatidine), and Pepcid Complete, a combination product containing the H_2RA famotidine and an antacid.

PPIs work by inhibiting the proton pump in the parietal cells of the stomach, thereby suppressing gastric acid secretion. Specifically, omeprazole inhibits gastric acid secretion by irreversible specific inhibition of the H^+/K^+ ATPase enzyme at the secretory surface of the lumen of the gastric parietal cell. When a PPI is discontinued, the ability to secrete gastric acid returns gradually over 3-5 days, as new proton pumps are generated. Accordingly, PPIs provide a long-lasting effect in reducing gastric acid secretion. The only PPIs currently approved for OTC use are Prilosec OTC (omeprazole delayed-release tablets 20 mg, formulated as omeprazole magnesium 20.6 mg),[1] omeprazole 20 mg delayed-release tablets, Zegerid OTC (omeprazole 20 mg, sodium bicarbonate 1100 mg), Prevacid 24HR (lansoprazole 15 mg), and lansoprazole 15 mg. P&G believes that one application is currently pending before the Agency seeking approval to market an OTC version of the prescription PPI Nexium® 20 mg (esomeprazole magnesium).

B. Prilosec OTC

Prilosec® (omeprazole) was the first PPI approved for prescription use; NDA 19-810 was approved in 1989. Prilosec OTC (omeprazole 20 mg as omeprazole magnesium 20.6 mg) was approved for OTC use on June 20, 2003 (NDA 21-229). The Prilosec OTC NDA, first submitted on January 27, 2000, was subjected to an extensive review, involving the presentation of data to

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[1] Omeprazole magnesium is the magnesium salt version of omeprazole, used for the OTC product because it facilitates tablet formulation. Tablet formulation was chosen for OTC status because it is more resistant to tampering and therefore suitable for OTC marketing. The tablet consists of multiple enteric coated pellets formulated with omeprazole magnesium. Omeprazole magnesium dissociates rapidly in water to form omeprazole and magnesium. A 20.6 mg dose of omeprazole magnesium is equivalent to a 20 mg dose of omeprazole. Omeprazole magnesium 20.6 mg tablets have a similar bioavailability profile to the 20 mg omeprazole capsules sold as prescription drugs. As FDA explained in response to a Citizen Petition objecting to the "Prilosec OTC" brand name, "Prilosec OTC contains 20.6 mg of omeprazole magnesium equivalent to 20 mg of omeprazole" and Prilosec and Prilosec OTC "contain the same active moiety, omeprazole, which is solely responsible for the products' identical pharmacological effect." *See* Ltr. to J. Mattingly from C. Ganley, pp. 7, 1, ftnt 1 (Jan. 21, 2005), Original Docket No. 2003P-0366/CP1, Regulations.gov Docket No. FDA-2003-P-0224, available at http://www.regulations.gov/#!documentDetail;D=FDA-2003-P-0224-0004.

two joint meetings of the Nonprescription Drugs Advisory Committee and the Gastrointestinal Drugs Advisory Committee on October 20, 2000 and June 21, 2002.

The Prilosec OTC NDA was supported by two multi-center, double-blind, randomized, double-dummy, parallel and placebo controlled studies involving 3,120 subjects with heartburn two or more days a week.[2] The studies were five weeks in duration, with a one week placebo run-in phase, a two week treatment phase, and a two week placebo follow up phase. The primary efficacy variable in both studies was no heartburn over the previous 24 hours (*i.e.*, complete prevention of heartburn or heartburn-free for a full day). This corresponds to a score of zero on widely used heartburn severity scales.[3]

Both clinical studies showed that Prilosec OTC resulted in a significant treatment effect during the first day. Almost 50% of subjects were heartburn-free for the full day after the first dose, compared to approximately 32% of subjects in the placebo group.[4] On day 14, the percentage of subjects in the treatment group reporting complete heartburn relief was over 70%.[5] During the two week treatment phase, subjects treated with Prilosec OTC had a significantly greater percentage of heartburn-free days than did the placebo-treated subjects.[6]

With respect to the secondary efficacy endpoints, over 80% of subjects reported no more than mild heartburn (corresponding to a score of 0 or 1 on the heartburn severity scale) on day 1 and almost 90% reported no more than mild heartburn across 14 consecutive days of dosing.[7]

II. In the Review and Approval of Applications for Authorization to Market PPIs for OTC Use, FDA Must Avoid Creating Artificial Labeling Distinctions

FDA has an obligation to apply its regulatory standards and requirements even-handedly among all similarly situated firms. In *Bracco Diagnostics, Inc. v. Shalala*, plaintiffs challenged

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[2] The studies submitted in support of NDA 21-229 are described in detail in the briefing document prepared in advance of the second advisory committee meeting convened to discuss the application. *See* Procter & Gamble Company, AstraZeneca LP, Omeprazole Magnesium Tablets, NDA No. 21-229, Advisory Committee Briefing Document (May 2, 2002) at pp. 43-59, available at http://www.fda.gov/ohrms/dockets/ac/02/briefing/3861b1_01_ProctorGamble-Zeneca.htm.

[3] While researchers use a variety of scales, each of which differ slightly, a score of zero typically corresponds to no heartburn/heartburn-free and a score of one corresponds to mild heartburn.

[4] Specifically, in one study (Study 171), 49.7% subjects were heartburn-free for the full day after the first dose vs. 32.6% in the placebo arm, and in the second study (Study 183), 46.8% of subjects were heartburn-free for the full day after the first dose vs. 32.1% in the placebo arm.

[5] In Study 171, 72% of subjects vs. 47.0% in the placebo arm, and in Study 183, 73% of subjects vs. 44.0% in the placebo arm.

[6] In Study 171 64.4% of subjects vs. 39.4% in the placebo arm, and in Study 183, 67.8% of subjects vs. 37.9% in the placebo arm.

[7] The day 1 results were: 81.0% vs. 71.6% in the placebo arm (Study 171) and 81.8% vs. 70.8% in the placebo arm (Study 183), and the 14 day results were: 88.6% vs. 75.9% (Study 171) in the placebo arm and 88.6% vs. 73.7% in the placebo arm (Study 183). Another secondary endpoint examined the percentage of subjects with no nocturnal heartburn following the first dose and across the 14 day treatment phase. In Study 171, the percentage of subjects with no nocturnal heartburn following the first dose was 78.4% vs. 70.4% in the placebo arm, and in Study 183, the results were 77.7% vs. 73.9% in the placebo arm (a difference that was not statistically significant). Over the 14 day treatment phase, 84.7% (Study 171) and 86.1% (Study 183) of subjects experienced no nocturnal heartburn vs. 74.5% (Study 171) and 75.4% (Study 183) in the placebo arm.

FDA's decision to subject their applications for injectable contrast imaging agents to different, more onerous, standards of review than were applied to another similar product.[8] The court granted plaintiffs' motions for preliminary injunction, holding that FDA's unexplained failure to treat similarly situated products in the same way was arbitrary and capricious in violation of the Administrative Procedure Act. The court determined that FDA could either regulate the products as drugs or devices, but could not impose disparate standards on the two products. In the words of the court, "[w]hat the FDA is not free to do, however, is to treat them dissimilarly and to permit two sets of similar products to run down two separate tracks, one more treacherous than the other, for no apparent reason."[9]

Likewise, all applications seeking approval to market PPIs in the OTC setting for treatment of frequent heartburn must be treated similarly. FDA should punctiliously avoid authorizing labeling distinctions that are based upon different standards or requirements than those imposed during the evaluation of the first such product – Prilosec OTC – or that will inadvertently convey to consumers that clinically meaningful differences between products exist, if such differences have not been demonstrated.

III. FDA Should Adopt Class "Use" and Dosing "Directions" Rather Than Permit Differing Label Statements, Unless Those Differing Statements Are Supported By Comparative Data Establishing Superior Efficacy

FDA should develop appropriate class labeling applicable to all OTC PPIs. All PPIs work in the same manner – by inhibiting the proton pump in the parietal cells of the stomach, thereby suppressing gastric acid secretion. None of the PPIs are intended for immediate treatment of heartburn or the prevention of heartburn brought on by foods or beverages. Similarly, none will reach full effect with the first dose in every patient, but instead the percentage of people achieving full heartburn relief will increase over a few days, and then plateau. Because all PPIs are indistinguishable from Prilosec OTC in these important respects, the labels for all PPIs sold OTC for treatment of frequent heartburn currently include—and should continue to include—the same type of statements currently included in the "Use" and "Directions" sections of the Prilosec OTC Drug Facts Box.

However, if data suggest that either the "Use" or "Directions" portion of the label for one or more other OTC PPIs could be expressed differently than is currently expressed on the Prilosec OTC label, the Agency should require data demonstrating such differences are clinically significant and do not explicitly or implicitly convey an impression as to relative safety or efficacy of PPIs that lacks adequate substantiation in the form of well-designed comparative studies and thereby is false or misleading.

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[8] 963 F.Supp. 20 (D.D.C. 1997)

[9] *Id. at* 27-8; *see also United States v. Diapulse Corp.*, 748 F.2d 56 (2d Cir. 1984) (holding that FDA must "apply its scientific conclusions evenhandedly" and cannot "'grant to one person the right to do that which it denies to another similarly situated'." (citation omitted)) ; *Allergan, Inc. v. Shalala*, No. 941223, 6 Food and Drug Rep. 389 (D.D.C. Nov. 10, 1994) (holding that FDA enforcement must be conducted in a fair and even handed manner against similarly situated parties; otherwise agency conduct is arbitrary and capricious in violation of the APA).

Differences in "Use" and "Directions," are likely to be misunderstood by consumers to mean that there are clinically significant differences between the products (*e.g.,* a product labeled with a shorter time period for full effect is preferable and/or more effective or potent than others).

Consumers may believe that the product labeled anything less than 1 to 4 days for full effect will provide relief more quickly than the other product. Some consumers may even assume that this more rapid relief is associated with potency, and conclude that product labeled to take less than 1 to 4 days for full effect is "stronger" medicine that will be more effective overall, even beyond the first several days of therapy.

Likewise, variations in the time of dosing each day could suggest to consumers that a longer-than-24-hour or shorter-than-24-hour dose interval is uniquely supported by an individual OTC PPI, compared to other PPIs on the market. Further, variations in the "Directions" for the 14-day course of treatment and the repeated 14-day courses could have a similar effect.

This potential for consumer confusion may be exacerbated by advertising claims emphasizing these differences in labeling to misleadingly suggest to consumers that they are clinically meaningful. Consumers are unlikely to appreciate the subtleties underlying differences in these label statements across OTC PPI products (*e.g.,* that the product labeled with the "before eating in the morning" statement may provide the same or greater symptom relief compared to the product without the statement). Accordingly, in the absence of comparative data establishing superior efficacy, it would be inappropriate for the Agency to approve language in the "Use" and "Directions" that differ across OTC PPIs.

IV. Differing Labeling Would Be Particularly Misleading In the Case of the Currently Pending OTC Switch Application for a PPI

P&G believes there is one pending application seeking approval to market OTC PPIs for treatment of frequent heartburn: Nexium 20 mg (esomeprazole magnesium).

P&G is not aware of any data suggesting that the OTC version of Nexium 20 mg would provide greater overall relief or relief to a greater percentage of consumers for frequent heartburn than Prilosec OTC.

In sum, it would be particularly inappropriate to approve any label text that is likely to convey to consumers that the OTC version of Nexium works faster, differently, or is otherwise more effective than Prilosec OTC. Thus, in the absence of comparative data demonstrating superior efficacy, P&G requests that the Nexium OTC label bear the same text currently in the Prilosec OTC label "Use" and "Directions" sections, or alternatively, that both labels include newly developed class labeling addressing these issues.

CONCLUSION

In reviewing pending and future applications to market OTC PPIs for relief of frequent heartburn, FDA must avoid approving label text that creates artificial distinctions between

products, and thereby facilitates false or misleading comparisons. In the absence of comparative data demonstrating superior efficacy, label text for all products in this pharmacological class must be consistent in order to avoid misleading consumers. P&G therefore requests that the Agency develop class labeling applicable to all over-the-counter PPIs or conform future approved labeling to that approved for Prilosec OTC.

ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion from the requirements of an environmental assessment or environmental impact statement pursuant to 21 C.F.R. § 25.31.

ECONOMIC IMPACT

An economic impact statement will be submitted if requested by the Commissioner, pursuant to 21 C.F.R. § 10.30(b).

Certification of The Procter & Gamble Company Under 21 U.S.C. § 355(q)(1)(H)

Pursuant to FDCA Section 505(q)(1)(H), the undersigned submits the following certification:

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following dates:

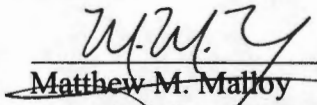
a. P&G has been aware of the standards and requirements imposed during review of NDA 21-229 for approval to market Prilosec OTC since June 20, 2003, the date of approval of the NDA;

b. P&G has been aware of the pending NDA seeking approval to market an OTC version of Nexium for heartburn since approximately August 2012; and

c. P&G is not aware of any other pending NDA seeking approval to market a PPI over-the-counter for heartburn.

If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: I am an employee of P&G and am making these representations on behalf of P&G as part of my responsibilities as an employee of P&G and am not being separately compensated for submitting this Petition. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



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