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November 17, 2011

BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
5630 Fishers Lane
Room 1061, HFA-305
Rockville, Maryland 20852

Re: Citizen Petition Regarding the Submission of ANDAs for Generic Prevacid®24HR (Lansoprazole) Capsules, 15 mg (OTC)

Dear Sir or Madam:

CITIZEN PETITION

Perrigo Company ("Perrigo") submits this Citizen Petition pursuant to section 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDC Act"), among other provisions of law, and the Food and Drug Administration's ("FDA's") implementing regulations set forth at 21 C.F.R. § 10.30.

I. ACTION REQUESTED

Perrigo requests that FDA:

(1) Refuse to receive, or otherwise rescind its receipt of any Abbreviated New Drug Application ("ANDA") for a generic version of Prevacid®24HR (lansoprazole) Capsules, 15mg, which is approved under New Drug Application ("NDA") No. 022327 for Over-the-Counter ("OTC") use, if the initial submission of such ANDA relies on bioequivalence studies conducted using ***prescription*** Prevacid® (lansoprazole) Delayed-Release Capsules, 15 mg, which is approved under NDA No. 020406; and

(2) Initiate notice-and-comment rulemaking with respect to any change in Agency policy concerning the acceptance of an ANDA for an OTC drug that does not contain bioequivalence data and information from studies conducted on the OTC Reference Listed Drug ("RLD"), but rather on a different listed drug; namely, the prescription version of such drug.

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FDA-2011-P-0840

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II. STATEMENT OF GROUNDS

A. Background

Lansoprazole is a proton pump inhibitor that FDA initially approved for prescription use on May 10, 1995 under NDA No. 020406 as Prevacid® Delayed-Release Capsules. Prevacid® Delayed-Release Capsules contain enteric-coated granules consisting of 15 mg or 30 mg of lansoprazole. Today, prescription Prevacid® is approved for myriad uses, including short-term treatment of active duodenal ulcer, *H. pylori* eradication to reduce the risk of duodenal ulcer recurrence, maintenance of healed duodenal ulcers, short-term treatment of active benign gastric ulcer, healing of NSAID-associated gastric ulcer, risk reduction of NSAID-associated gastric ulcer, gastroesophageal reflux disease, maintenance of healing of erosive esophagitis, and pathological hypersecretory conditions including Zollinger-Ellison Syndrome. NDA No. 020406 is listed in the "Prescription Drug Product List" section of FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book"), and the 30mg strength is identified as the RLD.

FDA approved NDA No. 022327 for Prevacid®24HR 15 mg Capsules on May 18, 2009 for nonprescription use for the treatment of frequent heartburn (occurring two or more days per week), and subsequently listed the drug product in the "OTC Drug Product List" of the Orange Book, identifying the drug as the RLD. Also listed in the Orange Book is a period of three-year new clinical investigation exclusivity – coded by FDA as "New Product" exclusivity – that is scheduled to expire on May 18, 2012, and that prevents the approval of an ANDA for a generic version of Prevacid®24HR until such date. See FDC Act § 505(j)(5)(F)(iii); 21 C.F.R. § 314.108(b)(4). With the approval of NDA No. 022327, both the 15 mg and 30 mg strengths remained prescription for their approved conditions of use under NDA No. 020406; however, the 15 mg strength switched to OTC status for the treatment of frequent heartburn.

The formulations of Prevacid®24HR 15 mg Capsules and Prevacid® Delayed-Release 15 mg Capsules are the same except for certain differences in appearance; namely, the addition of a black tamper-evident gelatin band (i.e., a "belly band") on Prevacid®24HR 15 mg Capsules that does not appear on Prevacid® Delayed-Release 15 mg Capsules because of the difference in prescription and OTC use of the drug products. See FDA, Summary Review, NDA No. 022327, at 3 (May 11, 2009).

Although FDA approved Prevacid®24HR on May 18, 2009, the drug product was not launched until six months later, on November 12, 2009. Perrigo believes that at least one manufacturer submitted an ANDA to FDA for a generic version of Prevacid®24HR containing the results of a bioequivalence study comparing its proposed Lansoprazole 15 mg Capsules to Prevacid® Delayed-Release 15 mg Capsules, and a request that FDA grant a biowaiver to relieve the sponsor from the need to conduct an in vivo bioequivalence study comparing its proposed drug product to the OTC version, Prevacid®24HR, for purposes of initially submitting such ANDA. Perrigo further believes that FDA received such an ANDA and granted a biowaiver, notwithstanding the fact that Prevacid®24HR 15 mg Capsules and Prevacid® Delayed-Release 15 mg Capsules are different listed drug products.

Perrigo understands that FDA's Office of Generic Drugs ("OGD") has recently established, without public comment, an internal policy of permitting an ANDA sponsor who is seeking approval of a generic version of a drug that has switched from prescription to OTC status, to use the prescription version of the drug for purposes of demonstrating bioequivalence and obtain a waiver from demonstrating bioequivalence to the OTC drug provided two conditions are met: (1) the prescription and OTC versions do not differ in formulation with the exception of appearance (such as the existence of a belly band); and (2) the OTC version has been launched (hereinafter "FDA/OGD Policy").

B. Analysis

1. The FDC Act and FDA's Implementing Regulations Require the Use of a Specific RLD for Bioequivalence Purposes

Under the FDC Act and FDA's implementing regulations, an ANDA sponsor must cite a particular "listed drug" – a "reference listed drug" – and must demonstrate that its proposed product is bioequivalent to the RLD. The term "listed drug" is defined in FDA's regulations to mean:

> a new drug product that has an effective approval under [FDC Act § 505(c)] for safety and effectiveness or under [FDC Act § 505(j)], which has not been withdrawn or suspended under [FDC Act §§ 505(e)(1) through (e)(5) or (j)(5)], and which has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness. Listed drug status is evidenced by the drug product's identification as a drug with an effective approval in the current edition of FDA's [Orange Book] or any current supplement thereto, as a drug with an effective approval. A drug product is deemed to be a listed drug on the date of effective approval of the application or abbreviated application for that drug product.

21 C.F.R. § 314.3(b). The term "reference listed drug" is defined in the same regulation to mean "the listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application." Id.

An applicant that meets the requirements under FDC Act § 505(j) for approval may reference FDA's finding of safety and effectiveness for the RLD, and need not repeat the extensive nonclinical and clinical investigations required for approval of a stand-alone NDA submitted under FDC Act § 505(b)(1).

FDC Act § 505(j)(2)(A) governs the content of an ANDA and states in relevant part that an application must contain:

> (i) information to show that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the new drug have been previously approved for a drug listed [in the Orange Book] (hereinafter in this subsection referred to as a "listed drug"); [and]

> (iv) information to show that the new drug is bioequivalent to the listed drug referred to in clause (i) . . . .

FDC Act § 505(j)(2)(A)(i), (iv).

Similarly, FDA's implementing regulations on the content and format of an ANDA state, in relevant part, that an ANDA "must refer to a listed drug," which ordinarily "will be the drug product selected by [FDA] as the reference standard for conducting bioequivalence testing," 21 C.F.R. § 314.94(a)(3), and that the ANDA must contain "[t]he name of the [RLD], including its dosage form and strength," id. § 314.94(a)(3)(i), "[a] statement that the conditions of use prescribed, recommended, or suggested in the labeling proposed for the drug product have been previously approved for the [RLD]," id. § 314.94(a)(4)(i), and "[i]nformation that shows that the drug product is bioequivalent to the [RLD] upon which the applicant relies," id. § 314.94(a)(7)(i). FDA's regulations at 21 C.F.R. §§ 320.21, 320.22, and 320.24 govern the requirements, methods, and procedures for a generic applicant to demonstrate bioequivalence for specific drug products, and state in pertinent part that an ANDA must contain "[e]vidence demonstrating that the drug product that is the subject of the [ANDA] is bioequivalent to the [RLD]." 21 C.F.R. § 320.21(b)(1).

FDA may refuse to receive an ANDA if the "abbreviated application is incomplete because it does not on its face contain information required under [FDC Act § 505(j)] . . . or § 314.94." 21 C.F.R. § 314.101(d)(3). And FDA may not approve an ANDA if "information submitted with the application is insufficient to show that each of the proposed conditions of use have been previously approved for the listed drug referred to in the application," FDC Act § 505(j)(4)(B), and if "information submitted in the application is insufficient to show that the drug is bioequivalent to the listed drug referred to in the application" id. § 505(j)(4)(F). Similarly, FDA's regulations state that the Agency will refuse to approve an ANDA if "[i]nformation submitted with the [ANDA] is insufficient to show that each of the proposed conditions of use has been previously approved for the listed drug referred to in the application," 21 C.F.R. § 314.127(a)(2), or if "[i]nformation submitted in the [ANDA] is insufficient to show that the drug product is bioequivalent to the listed drug referred to in the [ANDA]," id. § 314.127(a)(6)(i).

2. The FDA/OGD Policy is Contrary to the Law and FDA Policy

If FDA has, in fact, received an ANDA for a generic version of Prevacid®24HR 15 mg Capsules containing the results of bioequivalence testing in which the proposed new drug was compared to prescription Prevacid® Delayed-Release 15 mg Capsules as a result of the FDA/OGD Policy, then such receipt was improper. FDA must rescind receipt of such ANDA and require that it contain, upon ANDA submission, information demonstrating bioequivalence to the appropriate RLD – Prevacid®24HR 15 mg Capsules approved under NDA No. 022327.

What is clear from the statute and FDA's implementing regulations is that an RLD is a ***specific listed drug product***. That is, an RLD is a drug product approved under a specific NDA,

on a specific date, and with specific conditions of use, even though another pharmaceutically equivalent, and potentially bioequivalent, drug that is otherwise the same drug (with the possible exception of some appearance differences) is approved under a different NDA. In this case, Prevacid® Delayed-Release 15 mg Capsules cannot serve as an RLD for bioequivalence testing purposes for a generic version of Prevacid®24HR 15 mg Capsules. The products, despite their similarities, are different RLDs (each identified separately in the Orange Book as such), approved under different applications (NDA No. 020406 and NDA No. 022327), on different dates (May 10, 1995 and May 18, 2009), and with different conditions of use (e.g., prescription or OTC use).

Not only is the FDA/OGD Policy contrary to the plain text of the FDC Act and FDA's implementing regulations concerning the appropriate RLD, it is also contrary to FDC Act § 505(j)(2)(D), which states that an ANDA sponsor "may not amend or supplement an application to seek approval of a drug referring to a different listed drug from the listed drug identified in the application as submitted to the Secretary." FDC Act § 505(j)(2)(D)(i). The FDA/OGD Policy allows an ANDA sponsor to violate this provision by permitting an ANDA sponsor to demonstrate bioequivalence to a prescription version of a drug to satisfy the requirements of an ANDA submission, and at the same time allows that application to request that FDA grant a biowaiver from demonstrating bioequivalence to a different listed drug – the launched OTC RLD.

Permitting an ANDA sponsor to use Prevacid® Delayed-Release 15 mg Capsules for bioequivalence testing of a generic version of Prevacid®24HR 15 mg Capsules is also contrary to long-standing FDA policy. Many brand-name drug products marketed in the United States are marketed in foreign countries. ANDA sponsors have tried throughout the years to submit evidence to FDA that a drug product marketed in the United States and identified in the Orange Book as the RLD is the same drug product with the same specifications as a drug product marketed outside the United States, such that FDA could receive an ANDA containing bioequivalence testing data using the foreign drug product. FDA has flatly rejected such arguments and has maintained the position that an ANDA sponsor must demonstrate bioequivalence to the FDA approved RLD. FDA has defended this position by reason that the ANDA sponsor, which does not have visibility to certain chemistry, manufacturing and controls information in the RLD NDA, cannot certify without doubt that the United States and foreign marketed drug products are made at the same site, under the same process, with the same critical processing parameters, and with the same product specifications. Similar uncertainty exists with allowing an ANDA sponsor to rely on bioequivalence comparisons against the prescription version of a drug product that has switched to OTC status under a new NDA. Changes to any one of the parameters FDA has consistently used as a basis to reject requests to use a foreign marketed drug product in lieu of the FDA approved product could likewise affect the substantiation of bioequivalence. As such, FDA should not take any risk and should require ANDA sponsors to use the appropriate RLD – the approved OTC drug product – for bioequivalence testing purposes, and not a different drug – the approved prescription version of the switched drug.

The criterion in the FDA/OGD Policy that requires the launch of the OTC RLD before FDA will permit the submission of an ANDA containing bioequivalence testing data and

information to the prescription version of the drug product has no basis in law or regulation. There is simply no requirement that the date of ANDA submission must be pegged to the date of product launch. Instead, such an FDA-imposed requirement appears to be intended to shield the Agency from criticism from the OTC RLD NDA sponsor that FDA could accept an ANDA when there is no drug product on the market with which to demonstrate bioequivalence.

Imposing a launch date requirement for ANDA submissions would unnecessarily place new burdens on sponsors to continuously monitor news about product launches (provided, of course, such information is made public, since product launches may not be a matter of public record). It is likely to lead to significant controversy requiring judicial resolution.

As an initial matter, it is unclear what constitutes a product launch. If a small amount of product is released in one U.S. city but not nationwide, would that constitute a product launch for purposes of the FDA/OGD Policy? Moreover, FDA does not have a mechanism that requires a brand-name manufacturer to notify the Agency of a product launch, and it is unclear how FDA would validate a launch date against an ANDA submission date. Different ANDA sponsors may claim different launch dates supporting their submissions.

Although it is not the case with Lansoprazole 15 mg Capsules, when such a situation involves a Paragraph IV certification and eligibility for 180-day exclusivity, one company may claim one date constituted the product launch/ANDA submission date and another company another date. To secure first applicant status, and because a product launch could occur at any time after NDA approval, ANDA sponsors will likely resort to serial ANDA submissions. Such serial ANDA submissions would not only unnecessarily waste scarce FDA resources, but could unnecessarily complicate the user fee assessment and waiver processes that would be established by the Generic Drug User Fee Act if it is enacted next year.

Finally, a launch date criterion creates an uneven playing field for ANDA sponsors. Not all OTC product launches are nationwide, and therefore have the potential to advantage or disadvantage generic drug manufacturers based on the geographical outreach of individual companies.

3. FDA Must Amend its ANDA Regulations Through Notice-and-Comment Rulemaking Before Receiving an ANDA Pursuant to the FDA/OGD Policy

If FDA has received an ANDA for a generic version of Prevacid®24HR 15 mg Capsules pursuant to the FDA/OGD Policy as Perrigo suspects, then such ANDA was improperly received and such receipt should be rescinded, because FDA failed to employ notice-and-comment rulemaking prior to receiving such ANDA under a policy that effectively amended the rules governing generic drug submissions and approvals, and that treats similarly situated parties to divergent treatment in violation of the Administrative Procedure Act ("APA").

The APA requires notice of a proposed rule be published in the Federal Register and that such notice include the substance of and legal authority for the rule. See 5 U.S.C. § 553(b). In this case, FDA has not published any Federal Register notice of its intent to amend its

regulations to reflect the FDA/OGD Policy, let alone notice containing the substance of and legal authority for such a policy.

Although FDA has discretion in establishing the appropriate methods for a generic drug applicant to demonstrate bioequivalence for specific drug products, the Agency does not have unbounded authority to waive the ordinary requirement that an ANDA sponsor demonstrate bioequivalence to the appropriate RLD – here, Prevacid®24HR 15 mg Capsules approved under NDA No. 022327. "An agency is not allowed to change a legislative rule retroactively through the process of disingenuous interpretation of the rule to mean something other than its original meaning." Caruso v. Blockbuster-Sony Music Entm't Ctr. at the Waterfront, 193 F.3d 730, 737 (3d Cir. 1999) (internal quotations omitted); see also Shalala v. Guernsey Mem'l Hosp., 514 U.S. 87, 100 (1995) ("APA rulemaking would still be required if [an interpretive rule] adopted a new position inconsistent with any of the Secretary's existing regulations."). Rather, without notice-and-comment rulemaking, an agency may only issue an interpretation of a regulation that is "consistent with its language and original purpose." Nat'l Family Planning v. Sullivan, 979 F. 2d 227, 234 (D.C. Cir. 1992). When an "interpretation" of a rule "repudiates or is irreconcilable with [a prior legislative rule], the second rule must be an amendment of the first; and, of course, an amendment to a legislative rule must itself be legislative." Am. Mining Cong. v. Mine Safety & Health Admin., 995 F.2d 1106, 1109 (D.C. Cir. 1993).

The FDA/OGD Policy is flatly inconsistent with, and thus constitutes an amendment of, FDA's bioequivalence regulations, which require a demonstration of bioequivalence to a specific RLD. Before adopting this policy, however, FDA failed to employ the notice-and-comment procedures that the APA mandates for regulatory amendments. Unless and until FDA's regulations are properly amended, the APA bars FDA from applying the policy the Agency has apparently adopted.

FDA may not subject two similarly situated parties to divergent treatment; however, the FDA/OGD Policy does just that. The APA provides that a court may hold unlawful "agency action, findings, and conclusions found to be arbitrary, capricious, an abuse of discretion, or otherwise not in accordance with law." 5 U.S.C. § 706(2). Under this "arbitrary and capricious" standard, courts have held that agency action that treats similarly situated parties in a different manner is a violation of the APA. See Federal Election Comm'n v. Rose, 806 F.2d 1081, 1089 (D.C. Cir. 1986) ("[A]n agency's unjustifiably disparate treatment of two similarly situated parties works a violation of the arbitrary-and-capricious standard."); Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20, 28 (D.D.C.1997) ("What the FDA is not free to do, however, is to treat [similarly situated parties] dissimilarly and to permit two sets of similar products to run down two separate tracks, one more treacherous than the other."). The FDA/OGD Policy does not treat generic applicants uniformly. By arbitrarily setting the launch date as a criterion for ANDA submission, FDA creates an uneven playing field for some ANDA sponsors who because of their location may not learn of a product launch until well after the fact, thereby delaying a timely submission.

C. Conclusion

The FDA/OGD Policy is an ill-conceived interpretation of the FDC Act and FDA's regulations that has not gone through notice-and-comment rulemaking and otherwise violates the APA. Until such time that FDA implements such a policy as a regulation, FDA must refuse to receive, or otherwise rescind its receipt of any ANDA for a generic version of Prevacid®24HR 15 mg Capsules the initial submission of which relied on bioequivalence studies conducted using a different drug product; namely, prescription Prevacid® Delayed-Release 15 mg Capsules approved under NDA No. 020406.

III. ENVIRONMENTAL IMPACT

Perrigo claims a categorical exclusion from the requirements for an Environmental Assessment under 21 C.F.R. § 25.31(a) because the grant of this Citizen Petition would not have an effect on the environment.

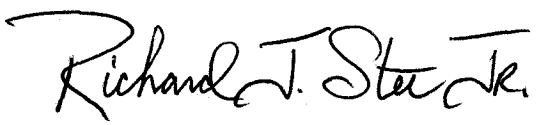
IV. ECONOMIC IMPACT

Information on the economic impact of the action requested by this Citizen Petition will be submitted if requested by FDA.

CERTIFICATION

Pursuant to the Act § 505(q)(1)(H), as added by Pub. L. No. 110-85, Perrigo makes 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 date: August 1, 2011. 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: Perrigo. 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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