DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

3686 '01 MAY -9 P2:04

MAY 2 2001

Elizabeth Shapar
7508A Spring Lake Drive
Bethesda, MD 20817

Dear Ms. Shapar:

This is in reply to your report to the Food and Drug Administrations's Office of Compliance regarding Perdiem fiber granules. Your report was referred to the Division of Over-the-Counter (OTC) Drug products on April 16, 2001. You stated that other psyllium laxative products, such as Metamucil, warn consumers to avoid using prescription products within two hours of using a laxative drug product because decreased absorption of the prescription product can occur. You noted that Perdiem had no such warning and you would like to see an appropriate warning on the product.

The laxative ingredient psyllium is currently being reviewed as part of FDA's review of the safety and effectiveness of OTC drugs. The OTC drug review is a 3-phase process: An advance notice of proposed rulemaking (based on an advisory panel's report (the Panel)), a notice of proposed rulemaking (tentative final monograph), and a final rule (final monograph or regulation). Active ingredients, rather than specific products, are reviewed.

The final monograph for OTC laxative drug products has not yet published. The Procter & Gamble Company has submitted a citizen petition to the Division of OTC Drug Products providing data to support its request that the agency include in the final monograph a drug-interaction precautionary statement for all laxatives. The Division reviewed the petition and intends to recommend to the Commissioner that the following warning be included in the laxative final monograph: "Ask a doctor or pharmacist before use if you are taking any other drug. Take this product 2 or more hours before or after other drugs. Laxatives may affect how other drugs work."

I have enclosed a copy of our November 6, 2000 response to the Proctor & Gamble citizen petition. I hope this information will be helpful.

Sincerely yours,

Arlene Solbeck

Arlene Solbeck, M.S.
Interdisciplinary Scientist
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

Enclosure 78N-036L

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

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NOV -6 2000

Nancy H. Allen
Manager, Regulatory Affairs, OTC Medicines
The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

Re: Docket No. 78N-036L
Comment No. CP22

Dear Ms. Allen:

This is in response to your citizen petition, dated March 28, 1996, and filed as Comment No. CP22 under Docket No. 78N-036L in the Dockets Management Branch. The petition requests that the agency reopen the administrative record and amend the OTC laxative tentative final monograph (TFM) to include the following drug-interaction precautionary statement for all laxatives: "Laxatives may affect how well other medicines work. If you are taking a prescription medicine by mouth, take this product at least 2 hours before or 2 hours after the prescribed medicine." The petition includes 36 published references (1965 to 1995) suggesting possible drug-drug interactions involving laxative agents in general, a review of drug-interaction reports from the FDA (1971-1995) and the WHO (1971-1993) databases, Proctor & Gamble's spontaneous postmarketing adverse event (AE) database (1986-1995) for Metamucil® (psyllium), precautionary label statements cited in current drug compendia, and a list of precautionary label statements on several types of laxative drug products marketed outside the United States. The petition also requests that this precautionary drug-laxative interaction label statement be included in the OTC laxative final monograph.

The Division of OTC Drug Products has reviewed the data and information submitted and concludes that the data are sufficient to include a precautionary drug-laxative interaction warning in the labeling for all OTC laxative drug products. We have the following comments: Of the 36 published references, 27 present evidence of possible drug interactions representing the following laxative classes: bulk-forming, hyperosmotic, lubricant, saline, stimulant, and stool softener laxatives. Nine references were excluded because they were abstracts/reviews of articles already included in the submission; studies sponsored by Procter & Gamble; studies involving psyllium in combination with other laxatives; *in vitro* or animal studies; or interactions involving excipient compounds. Although the reports are varied in terms of design, patient population, and analytical detail, on balance, this comprehensive literature review suggests that by altering gastrointestinal motility, laxative agents, as a therapeutic class, have the potential for

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modifying the systemic bioavailability (C-max, T-max and/or AUC) of co-administered medications.

The FDA database contained 6 reports with saline laxatives, 5 with bulk-forming laxatives, and one each with stimulants and stool softeners. The WHO database contained 8 reports involving possible psyllium interactions. There were no reports in the WHO data base involving other laxative ingredients. In general, these reports provide some weak support for drug-laxative interactions. Besides the paucity of information and varying quality with respect to ascertainment, there are other biases inherent in post-marketing surveillance data. For example, the number of cases reported may vary according to the length of time a product has been marketed or with the reporting environment (e.g., the level of publicity given a drug or an adverse event). The number of patients at risk or the patient exposure to drug in terms of days or months of therapy is also an unknown, or can only be crudely estimated.

Procter & Gamble's survey of the AE database for Metamucil® (psyllium) resulted in 14,004 reports for the 1986-1995 period. Fifty-one of these reports suggested that psyllium may interfere with concomitantly administered oral medications. Using the criteria of positive dechallenge, number and indications of concomitant medications taken, and unexpected AE's for which there was no other apparent explanation, the strength of association between the AE and a drug-drug interaction involving the laxative was classified as strong, moderate, possible, or indeterminate. Results were as follows: 5 reports were classified as strong, 9 as moderate; 20 as possible; and 17 as indeterminate. In general, the AE reports included clinically important conditions such as seizures, hypertension, diabetes, asthma, and ineffective anticoagulation. Both tablet and capsule dosage forms and immediate and sustained-release characteristics were implicated. Many of the patients were older adults (26 of the 33 individuals whose age was reported were at least 60 years old.)

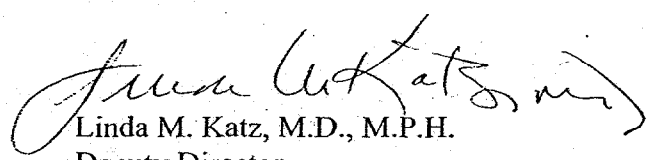
We have also considered the precautionary statements regarding drug-laxative interactions in current drug information compendia and on the labels of laxative drug products marketed in countries in support of the recommended labeling proposal. Based on all the data reviewed, we believe that a precautionary statement, specifically detailing the timing of laxative administration and concomitant drug therapy, should be included in the labeling of all OTC laxative drug products.

In regard to the reopening of the administrative record for submission of data and information currently being reviewed by the agency, it should be noted that the administrative record for OTC laxative drug products closed March 17, 1986. Your petition was not submitted until March 29, 1996. In accordance with 21 CFR 330.10(a)(7)(v), new data and information submitted after closing of the administrative record, but prior to the establishment of a final monograph will be considered after a final monograph has been published, unless good cause has been shown that warrants earlier consideration. The Division believes that good cause to warrant earlier consideration has been shown. Therefore, the Division intends to recommend to the Commissioner that the agency respond to your petition by including in the laxative final monograph the following warning: "Ask a doctor or pharmacist before use if you are taking any other drug. Take this product 2 or more hours before or after other drugs. Laxatives may affect how other drugs work."

The Division also intends to recommend to the Commissioner that the agency allow a 90-day period for interested persons to comment on the warning. The agency will respond to these comments and revise the warning, if necessary, before the effective date of the final monograph for OTC laxative drug products.

If you have any questions, please refer to the docket number above and submit all inquires in triplicate, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

Sincerely yours,



Linda M. Katz, M.D., M.P.H.
Deputy Director
Division of OTC Drug Products,
Office of Drug Evaluation V
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