

Procter & Gamble

The Procter & Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road, Mason, Ohio 45040-9462

January 20, 2004

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

RE: Comments to Docket No. 78N-036L; Laxative Drug Products for Over-the-Counter
Human Use

Dear Sir or Madam:

Enclosed are three copies of comments from Procter & Gamble on data and information previously submitted to the Division of Dockets Management after the administrative record closed, which the agency has now accepted for review (*Federal Register*: 68, No. 204, 60302-60304, October 22, 2003).

Procter & Gamble recommends that the Food and Drug Administration (FDA) accept the enclosed comments regarding:

- (1) active ingredients to be included in the final OTC laxative monograph;**
- (2) wording of the Drug Interaction warning statement for laxative products; and,**
- (3) terminology for Statement of Identity and Indications for bulk-forming laxative products.**
- (4) Additionally, in light of new information regarding a submission that was made within a comment period, Procter & Gamble respectfully requests that the agency review the method by which divided doses of bulk-forming laxative products were determined.**

Sincerely yours,

The Procter & Gamble Company



P. LaMont Bryant, Ph.D.

Regulatory Affairs Manager, Personal Health Care

78N-036L

January 20, 2004

Comments by Procter & Gamble (P&G) to Docket No. 78N-036L, Laxative Drug Products for Over-the-Counter Human Use, in response to Proposed rule; reopening of the administrative record (*Federal Register*: 68, No. 204, October 22, 2003)

Following are P&G's comments on data and information previously submitted to the Division of Dockets Management after the administrative record closed, which the agency has now accepted for review. P&G requests the Food and Drug Administration (FDA) accept for filing these comments regarding the tentative final monograph (TFM) for laxative products, Docket No. 78N-036L (*Federal Register*: 2124, January 15, 1985), prior to its publication as a final monograph.

1) Re: Submission to Docket No. 78N-036L (October 23, 2000) from Consumer Healthcare Products Association (CHPA), in response to FDA's request for comments on several topics related to psyllium (Attachment 1)

In response to FDA's July 28, 1995 letter to CHPA stating that the final laxative monograph will only contain active ingredients that have USP monographs (*plantago* seed, psyllium husk and psyllium hydrophilic mucilloid for oral suspension), CHPA's 2000 letter pointed out that psyllium hydrophilic mucilloid for oral suspension is a finished product rather than an active ingredient. The active ingredient is actually psyllium hydrophilic mucilloid. CHPA requested that, in addition to *plantago* seed and psyllium husk, psyllium hydrophilic mucilloid and psyllium (hemicellulose) be kept as active ingredients in the final laxative monograph.

Since CHPA's 2000 submission to the docket, a USP monograph has published (PF Vol. 30) for psyllium (hemicellulose), which is currently being reviewed (Attachment 2). It is expected to finalize January 1, 2005. Consequently, P&G supports CHPA's comment and requests that psyllium (hemicellulose) be maintained as an active ingredient in the final laxative monograph.

2) **Re: FDA Response (Attachment 3) to Submission to Docket No. 78N-036L (Comment No. CP22, March 28, 1996) from P&G; Citizen Petition requesting the agency to include a drug-interaction precautionary statement for all laxatives**

In the 1996 Citizen Petition, P&G proposed the following precautionary statement: “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 agency indicated in their response letter to P&G (November 6, 2000) that they intended to recommend to the Commissioner that the agency include the following warning 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.”

P&G has reason to propose an alternate statement. According to 21 CFR 201.66 (c) (v), a drug-drug interaction statement must include the words, “**Ask a doctor or pharmacist before use if you are...**”, followed by the drug-drug interaction warning. To be consistent with this approach, P&G requests the agency recommend the following statement:

“Ask a doctor or pharmacist before use if you are taking a prescription drug. Laxatives may affect how other drugs work. Take this product 2 or more hours before or after other drugs.”

P&G wants to assure that the warning is appropriate to the issue. Although it is possible that OTC drugs have a potential to interact with laxative medications, P&G’s proposed precautionary statement selectively addresses prescription medicines for four reasons.

First, specifying ‘prescription drug’ would focus consumers’ (and, subsequently, health care professionals’) attention on those medications used in treating medically significant illnesses or conditions, where avoidance of drug interaction would be most critical. There is precedence in the market place for specifying prescription drugs in the drug-drug interaction warning, e.g., Metamucil products and Phillips’ MO. However, several laxative products on the market do currently use FDA’s proposed warning statement.

Second, although some OTC medicines are used in treating medically significant conditions (aspirin use in cardiovascular disease is most frequently cited), in these cases the OTC medications are also prescribed by a physician, and therefore, may be thought of by the consumer in the same context as prescription drugs. Regardless, the proposed warning statement does provide direction that the laxative product should be taken 2 or more hours before or after **other drugs**; thus, consumers should not need to check with a doctor or pharmacist for every drug if they follow this direction.

Third, as shown in the Citizen Petition, published literature supporting the recommendation for a precautionary drug interaction statement on laxative products primarily consists of cases involving prescription drugs.

Fourth, as shown in the Citizen Petition, the vast majority of cases from P&G's spontaneous Adverse Event data base suggested drug interaction involved prescription drugs.

3) Re: Submission to Docket No. 78N-036L (Comment No. C144, November 23, 1992) from Nonprescription Drug Manufacturers Association (NDMA)

The NDMA (now CHPA) submission addressed physician and consumer understanding of various terms pertaining to the statement of identity (SOI) of OTC laxative drug products containing fiber. P&G seeks clarification in the final monograph of the agency's response to this submission (Attachment 4), verifying that the phrase, "fiber laxative" is a viable alternative to "bulk-forming laxative" as a SOI and that "Fiber therapy for relief of occasional constipation [which may be followed by "(irregularity)"]" is a viable alternative to the indication, "For relief of occasional constipation" [which may be followed by "(irregularity)"].

The agency's response included the following paragraph, which indicates "fiber laxative" could be used as a SOI: "Based on the information contained in your submission, the Office of OTC Drug Evaluation concludes that the data generated from implementation of the proposed protocols would not provide sufficient evidence to change the statement of identity of bulk forming laxatives to "Fiber therapy for Irregularity." The term "Fiber therapy for irregularity" implies that the drug corrects, avoids, or prevents irregularity; in our view, such claims would require the submission of clinical studies. Terms such as "Bulk-forming laxative" or "Fiber laxative" when used as statements of identity would not require such clinical proof because these terms do not imply prevention or long term correction of disease."

From the preceding paragraph, P&G ascertains that “fiber laxative” may be used as an alternative to “bulk-forming laxative”, which is listed as the SOI in 21 CFR § 334.52 (a). P&G requests that the term “fiber laxative” be included in the final laxative monograph.

P&G deems there is an error in the following sentence found in the first full paragraph on page 5 of the agency’s response: “However, we might consider including the term “fiber laxative” as an optional (allowable) indication for bulk-forming laxatives in the final monograph as follows: “Fiber therapy for relief of occasional constipation” [which may be followed by “(irregularity)”. P&G believes the term “fiber laxative” was used inadvertently and that the term “fiber therapy” was intended. P&G seeks clarification that this was an error and requests that the following indication be included in the final laxative monograph: “Fiber therapy for relief of occasional constipation” [which may be followed by “(irregularity)”. This is in addition to the indication, “For relief of occasional constipation” [which may be followed by “(irregularity)”.]

Procter & Gamble respectfully requests the agency review the following comments regarding the method by which divided doses of bulk-forming laxative products were determined.

4) Re: Submission to Docket No. 78N-036L (November 26, 1986) from P&G, regarding directions for use of bulk-forming laxatives (Attachment 5)

P&G requests the agency reassess the method by which the minimum divided doses for bulk-forming laxatives were determined in the proposed rule (*Federal Register*: 51, No. 190, October 1, 1986). P&G proposes that the method used to derive the minimum divided dose for psyllium products ought to be equally applied to all other active ingredients. There were inconsistencies in this proposal pertaining to the minimum doses specified for the divided dose ranges of actives. For all actives except psyllium the newly established minimum divided doses are below the established minimum effective total daily dose cited in the TFM. Whether these actives are administered as a single dose or in multiple doses, the potential exists that all actives, except for psyllium, could be administered at subtherapeutic dose levels.

Since this proposed rule was published, additional bulk-forming laxative products have entered the market. Based on the fact that the minimum divided doses of active do not correspond to the minimum effective daily doses specified in the TFM, the potential exists that the dose levels for these products are not effective. Therefore, P&G reiterates its request that the agency assure that the dose levels that have been recommended for bulk-forming laxative active ingredients besides psyllium are effective dosages.

Respectfully submitted,

P. LaMont Bryant, Ph.D.

Regulatory Affairs Manager, Personal Health Care

A handwritten signature in cursive script that reads "Paul L. Bryant".

The Procter & Gamble Company

8700 Mason-Montgomery Road

Mason, Ohio 45040-9462

Phone: 513-622-1830

Attachment 1

Submission to Docket No. 78N-036L (October 23, 2000) from Consumer Healthcare Products Association (CHPA), in response to FDA's request for comments on several topics related to psyllium



Producers of Quality
Nonprescription Medicines and
Dietary Supplements for Self-Care

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION

Formerly Nonprescription Drug Manufacturers Association

October 23, 2000

Charles Ganley, M.D.
Director, Division of Over-the-Counter Drug Products
Center for Drug Evaluation and Research (HFD-560)
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857-1706

Re: Docket No. 78N-036L

Dear Dr. Ganley:

Some time ago FDA asked the Laxative Task Group of the Consumer Healthcare Products Association (CHPA, formerly the Nonprescription Drug Manufacturers Association) to comment on the agency's determination and comments pertaining to psyllium (see attached letter from William E. Gilbertson, Pharm.D., July 28, 1995, regarding Docket No. 78N-036L). The agency specifically sought comments on the following topics:

1. Methodology to more accurately assay the amount of hydrophilic mucilloid, for a possible revision of USP monograph standards for psyllium preparations;
2. Change in dosage ranges;
3. Assessment of need for name changes so names are appropriate and consistent; and
4. Review of compendial purity standards for *plantago* seed, psyllium husk, and psyllium hydrophilic mucilloid for oral suspension to ensure consistent and reasonable standards.

This letter provides the CHPA Psyllium Subgroup's responses on each of these topics.

Assay of hydrophilic mucilloid

FDA is requesting that manufacturers of psyllium products work with the USP Convention to possibly revise the monograph standards for psyllium preparations to more accurately measure hydrophilic mucilloid content, i.e., to consider including measurements of mucilloid content in gram-weight (the compendial standards measure the mucilloid content using swell volume methodology) and/or converting the swell volume to gram-weight.

Charles Ganley, M.D.
October 23, 2000
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CHPA members who manufacture over-the-counter (OTC) psyllium products consider the current swell volume methodology sufficient for measuring the content of psyllium husk and fragmented psyllium husk for oral suspension. The swell volume test is well established with much historical data; it is a test that manufacturing plants can use very effectively. Company studies demonstrate that swell volume is precise (precision is 1.6% Relative Standard Deviation).

In addition, a CHPA member company is working to establish a USP monograph for a finished product, "Psyllium Hydrophilic Mucilloid Granules," a granular mixture of psyllium husk and seed. This proposed product monograph also relies on swell volume methodology as a measure of psyllium content. The swell volume assay contained in the proposed Psyllium Hydrophilic Mucilloid Granules monograph is similar to the swell volume test used in the current USP monograph for Psyllium Hydrophilic Mucilloid for Oral Suspension, but differs to accommodate differences in the product formulations. The swell volume assay for Psyllium Hydrophilic Mucilloid Granules was reviewed during a 1999 FDA inspection of the manufacture and was found to be acceptable.

We believe there is confusion around the term "psyllium hydrophilic mucilloid." FDA's July 28, 1995 letter to CHPA stated that "because the final (laxative) monograph will only contain active ingredients that have USP monographs, only *plantago* seed, psyllium husk and psyllium hydrophilic mucilloid for oral suspension would be included at this time." We would like to point out that the USP monograph defines Psyllium Hydrophilic Mucilloid for Oral Suspension as "a dry mixture of Psyllium Husk with suitable additives" (see attached USP monograph). This describes a finished product and thus would not be included in the OTC laxative monograph, which is specific to active ingredients. "*Plantago* Seed" and "Psyllium Husk" USP monographs refer to active ingredients.

CHPA members consider the active ingredient in "Psyllium Hydrophilic Mucilloid for Oral Suspension" to be "psyllium hydrophilic mucilloid" and would like the option of keeping this and "psyllium (hemicellulose)" as active ingredients in the final laxative monograph. Clarity is required around the names and active ingredient definitions (see Appendix).

Change in dosage ranges

FDA proposes dosages for psyllium-containing products be based on the levels of mucilloid that can be extracted from psyllium seeds. The FDA is proposing 2.5-14 g of psyllium hydrophilic mucilloid for a daily dosage for adults and children 12 years of age and over and 1.25-7 g for children 6 to under 12 years of age and a maximum daily dosage of 30 g of *plantago* seed (as opposed to 2.5-30 g and 1.25-15 g, for products containing any psyllium ingredient identified in 334.10 (f) in the Tentative Final Monograph [TFM]). The agency states that a daily dose of 2.5-14 g provides for a range that generally reflects dosages for mucilloid content that are suggested for use for occasional constipation.

Charles Ganley, M.D.
October 23, 2000
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We recommend the dose ranges stated in the TFM (2.5-30 g of psyllium for a daily dosage for adults and children 12 years of age and over and 1.25-15 g for children 6 to under 12 years of age) remain in effect. Support for this is the health claim for soluble fiber from psyllium, wherein the agency disagreed with comments that argued that limits should be placed on permissible levels of psyllium husk in foods (*Federal Register*, Vol. 63, No. 32, February 18, 1998, pp. 8103-8121). The agency stated in this reference that a preliminary review of the Kellogg Company's GRAS affirmation petition revealed that it contains significant evidence supporting the safety of the consumption of up to 25g/day of psyllium husk in a variety of food categories (p. 8112). Also, the 1993 Life Sciences Research Office (LSRO) psyllium husk report concluded a daily intake of up to 25 g/d of psyllium husk is safe (LSRO. The Evaluation of the Safety of Using Psyllium Seed Husk as a Food Ingredient. Bethesda, MD., December 1993).

Need for name changes

FDA suggested the USP Convention assess the need for official name changes so the names are appropriate and consistent.

CHPA agrees name changes are needed to assure consistency. Psyllium is defined in both *The American Heritage College Dictionary* and *Webster's Ninth New Collegiate Dictionary*, while the word "plantago" is found in neither. Thus, we think consumers are unlikely to be familiar with the term "plantago" and recommend that all products containing psyllium be labeled with the word "psyllium."

We recommend that the USP Monograph currently entitled "*Plantago Seed*" be renamed "Psyllium Seed." We also recommend the psyllium active ingredients in the OTC laxative monograph that are now called "Plantago ovata husks" and "Plantago seed" be called "Psyllium husk" and "Psyllium seed."

Compendial purity standards

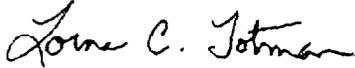
According to FDA, one laxative manufacturer noted that different grades of psyllium lead to inconsistencies in dosing. The information in the letter from Rowell Laboratories was misinterpreted. FDA stated in their letter to CHPA, "As an example, the manufacturer stated that a psyllium-containing product containing a 50% grade of psyllium would require a dosage of approximately 7 g in order to be comparable to a dosage of 3.5 g of psyllium at an 85% to 95% purity level." Actually, the Rowell letter said drug products are available that contain 50% psyllium (not psyllium that is 50% pure). The only reason one would need to take more grams of the product is because excipients are present.

CHPA agrees that a review of compendial purity standards is needed to ensure consistent and reasonable standards. *Plantago seed* (psyllium seed) currently does not have the same purity standards as husk, and wherever feasible the standards applicable to husk should be applied to seed, e.g., microbial limits.

Charles Ganley, M.D.
October 23, 2000
Page 4 of 5

Please let me know if you or others at FDA have questions about any of these comments regarding psyllium as an active ingredient in OTC laxative products.

Sincerely yours,



Lorna C. Totman, Ph.D., DABT
Director of Scientific Affairs

Appendix: Definitions

Attachments: A—Letter from Gilbertson, FDA, to Soller, NDMA, July 28, 1995
B—USP monographs for Psyllium Hydrophilic Mucilloid for Oral Suspension, Plantago Seed, and Psyllium Husk

cc: FDA Dockets Management Branch (3 copies)

LT/et

Charles Ganley, M.D.
October 23, 2000

Appendix

Definitions

Plantago seed - cleaned, dried, ripe seed, with psyllium husk constituting approximately 15-35% of the seed by weight; known in commerce as (Spanish or French or Blonde) Psyllium Seed or as Indian *Plantago* Seed.

Psyllium seed - synonymous with *plantago* seed. Psyllium is the preferred term in the United States.

Psyllium husk - cleaned, dried seed coats; the active ingredient in most psyllium bulk-forming laxatives.

Psyllium seed husk - synonymous with psyllium husk.

Psyllium hydrophilic mucilloid for oral suspension - a dry mixture of psyllium husk with suitable excipients or additives (bulk-forming laxative product).

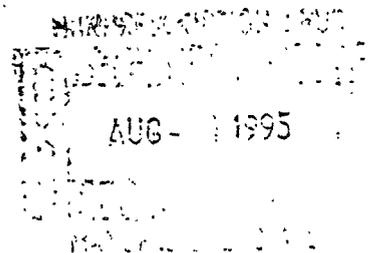
Mucilage - the water-soluble intracellular polysaccharide in psyllium husk.



July 28, 1995

Food and Drug Administration
Rockville MD 20857

R. William Soller, Ph. D.
Senior Vice President and
Director of Science & Technology
Nonprescription Drug Manufacturers Association
1150 Connecticut Avenue, NW
Washington, D.C. 20036



Re: Docket No. 78N-036L

Dear Dr. Soller:

As you are aware, we are in the process of developing the final rule for over-the-counter (OTC) laxative drug products. In response to the tentative final monograph (TFM) (50 FR 2124) and amended TFM for OTC laxative drug products (51 FR 35136), two manufacturers questioned the appropriateness of the proposed daily dosage of 2.5 to 30 g for psyllium-containing preparations. One manufacturer stated that these dosages were inconsistent with the dosing ranges of marketed psyllium-containing laxative drug products and with dosages provided in the scientific literature. The manufacturer also noted that the various available commercial grades of psyllium (i.e., 50, 85, and 95 percent) lead to inconsistencies in dosing. As an example, the manufacturer stated that a psyllium-containing product containing a 50 percent grade of psyllium would require a dosage of approximately 7 g in order to be comparable to a dosage of 3.5 g of psyllium at an 85 to 95 percent purity level. Another manufacturer requested that the proposed divided dosing range in the amended TFM should be sufficiently flexible to accommodate its marketed psyllium-containing laxative drug product.

Based on a review of the scientific literature and our survey of the OTC marketplace, we also have concerns about the appropriateness of the Panel's recommended daily dosage of 2.5 to 30 g for all psyllium-containing preparations.

In the tentative final monograph (TFM) for OTC laxative drug products, the agency agreed with the Panel's recommended daily dosages of 2.5 to 30 g for psyllium preparations, which included plantago seed, plantago ovata husks, psyllium (hemicellulose), psyllium hydrophilic mucilloid (psyllium hydrocolloid), psyllium seed, psyllium seed (blond), and psyllium seed husks (50 FR 2154). However, because the final monograph will only contain active ingredients that have U.S.P. monographs, only plantago seed, psyllium husk, and psyllium hydrophilic mucilloid for oral suspension would be included at this time.

Based upon our review of the scientific literature and our survey of the OTC marketplace for psyllium-containing laxative drug products, we determined that the primary constituent responsible for the bulk-forming laxative action is psyllium hydrophilic mucilloid. We also found that most OTC marketed psyllium preparations list the psyllium hydrophilic mucilloid or husks (which is the primary source of the mucilloid) as the active ingredient and that dosages are based primarily on the content of psyllium hydrophilic mucilloid.

R. William Soller, Ph. D.

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We have determined from articles in the literature (copies enclosed) that the maximum percentage (approximate 32 percent) of the mucilloid that can be extracted from equivalent daily dosages of psyllium (plantago) seeds (7 to 45 g) found in the literature references is approximately 2.24 to 14.4 g of the hydrophilic mucilloid. From these approximate dosage ranges, we have concluded that the Panel's minimum daily dosage of 2.5 g (40 FR 12908) is appropriate for psyllium hydrophilic mucilloid and that allowing a maximum daily dose of 14 g provides for a daily dosing range (i.e., 2.5 to 14 g) that generally reflects dosages for mucilloid content found in the OTC drug marketplace for use for the relief of occasional constipation. We note that although the literature information pertaining to the 32 percent extraction of mucilloid from seeds was published in 1932, based on a recent telephone conversation with Dr. Scrivivasan of the United States Pharmacopeial Convention (U.S.P.C.), that information still appears to be applicable. However, we are interested in knowing whether there is any improved methodology (since 1932) to more accurately assay the amount of the hydrophilic mucilloid extracted.

In the final monograph, we plan to base the dosages for psyllium-containing products on the content of psyllium hydrophilic mucilloid for a daily dosage of 2.5 to 14 g for adults and children 12 years of age and over and 1.25 to 7 g for children 6 to under 12 years of age. We believe that this dosing range based on psyllium hydrophilic mucilloid content provides sufficient flexibility to generally accommodate the existing OTC psyllium-containing laxative drug products. We also consider the Panel's recommended maximum daily dosage of 30 g as still applicable to plantago seed. Therefore, the dosages for plantago seed would be based on the hydrophilic mucilloid content with a maximum daily dosage limitation of 30 g of the seed. We are requesting your comments regarding these dosage ranges.

We have also sent a letter to the U.S.P.C. requesting its review and comment on the U.S.P. monographs for plantago seed, psyllium husks, and psyllium hydrophilic mucilloid for oral suspension (copy enclosed). Because the compendial standards only measure the hydrophilic mucilloid content using the swell volume methodology, we are also requesting the U.S.P.C. to consider using or including equivalent content measurements in gram-weights. We are asking for your association's assistance in requesting that manufacturers work with the U.S.P.C. to revise the monograph standards for psyllium preparations to more accurately measure hydrophilic mucilloid content and consider including equivalent measurements in gram-weight and to assess the need for official name changes so that the names are appropriate and consistent. We are also recommending that the compendial purity standards for plantago seed and psyllium hydrophilic mucilloid be reviewed and evaluated to ensure consistent and reasonable standards. We request that manufacturers forward to the U.S.P.C. appropriate information on any improved analytical methods to assay and measure psyllium hydrophilic mucilloid content. This appears to be an area that your Laxative Task Force may want to review.

We also would appreciate any comments regarding the agency's determinations and comments pertaining to psyllium. Because we want to consider this information in preparing the final monograph, we would appreciate an expeditious response.

R. William Soller, Ph. D.

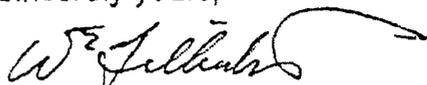
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All comments and information should be submitted in three copies, identified with the docket number shown at the beginning of this letter, to the Dockets Management Branch, (HFA-305), Food and Drug Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

Should you have any questions, please contact Gloria Chang of my staff at 301-594-0897.

Your assistance will be greatly appreciated.

Sincerely yours,



William E. Gilbertson, Pharm.D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research

Enclosures

USP Monographs

2P33730

PSYLLIUM HYDROPHILIC MUCILLOID FOR ORAL SUSPENSION

>> **Psyllium** Hydrophilic Mucilloid for Oral Suspension is a dry mixture of **Psyllium** Husk with suitable additives.

PACKAGING AND STORAGE -- Preserve in tight containers.

IDENTIFICATION -- Microscopically, it shows the presence of fragmented **Psyllium** Husk, as described for Histology -- Husk in the section, Botanic characteristics, under **Psyllium** Husk.

MICROBIAL LIMITS <61> -- It meets the requirements of the tests for absence of *Salmonella* species and of *Escherichia coli*.

SWELL VOLUME -- Transfer 250 mL of simulated intestinal fluid TS without enzymes to a glass-stoppered, 500-mL graduated cylinder. Gradually, with shaking, add an amount of **Psyllium** Hydrophilic Mucilloid for Oral Suspension, equivalent to 3.5 g of **psyllium** husk, and shake until a uniform, smooth suspension is obtained. Dilute with the same fluid to 500 mL. Shake the cylinder for about 1 minute every 30 minutes for 8 hours. Allow the gel to settle for 16 hours (total time 24 hours). Determine the volume of the gel: it is not less than 110 mL.

USP Monograph

2P17500
PLANTAGO SEED

>> Plantago Seed is the cleaned, dried, ripe seed of *Plantago psyllium* Linne, or of *Plantago indica* Linne (*Plantago arenaria* Waldstein et Kitaibel), known in commerce as Spanish or French *Psyllium* Seed; or of *Plantago ovata* Forskal, known in commerce as Blond *Psyllium* or Indian *Plantago* Seed (Fam. Plantaginaceae).

PACKAGING AND STORAGE -- Preserve in well-closed containers, secure against insect attack (see Vegetable and Animal Drugs -- Preservation in the General Notices).

BOTANIC CHARACTERISTICS --

Unground *Plantago psyllium* Seed -- Ovate to ovate-elongate, concavo-convex; mostly from 1.3 to 2.7 mm in length, rarely up to 3 mm.

and from 600 μ m to 1.1 mm in width. It is light brown to moderate brown, darker along the margin, and very glossy; the convex dorsal surface exhibiting a lighter colored longitudinal area extending nearly the length of the seed and representing the embryo lying beneath the seed coat, and showing a sometimes indistinct transverse groove nearer the broader end. The concave ventral surface has a deep cavity, in the center of the base of which is an oval, yellowish white hilum.

Unground *Plantago indica* Seed -- Ovate-oblong to elliptical, concavo-convex; from 1.6 to 3 mm in length and from 1 to 1.5 mm in width. Externally it is dark reddish brown to moderate yellowish brown, occasionally somewhat glossy, often dull, rough, and reticulate; the convex dorsal surface having a longitudinal lighter colored area extending lengthwise along the center and beneath the seed coat, and a median transverse groove, dent, or fissure. The ventral surface has a deep concavity, the edges somewhat flattened and frequently forming a sharp indented angle with the base of the cavity, the latter showing a light colored oval hilum.

Unground *Plantago ovata* Seed -- Broadly elliptical to ovate, boat-shaped, from 2 to 3.5 mm in length and from 1 to 1.5 mm in width. It is pale brown to moderate brown with a dull surface, the convex surface having a small, elongated, glossy brown spot. The concave surface has a deep cavity, in the center of the base of which occurs a hilum covered with a thin membrane.

Odor and taste -- All varieties of *Plantago* Seed are nearly odorless.

Histology -- *Plantago* Seed is reniform in median transverse sections.

Its seed coat has a colorless epidermis of mucilaginous cells whose radial and outer walls break down to form layers of mucilage when

brought into contact with water, and a reddish brown to yellow pigment layer in the seeds of *Plantago indica* and *Plantago psyllium*, a broad endosperm with thick-walled outer palisade cells, and irregular inner endosperm cells; and a straight embryo extending lengthwise through the center. The endosperm and embryo cells contain fixed oil and aleurone grains, the latter being rounded, oval, pyriform, or irregularly shaped, from 2 to 8 μm in diameter.

WATER ABSORPTION -- Place 1 g of *Plantago Seed* in a 25-mL graduated cylinder, add water to the 20-mL mark, and shake the cylinder at intervals during 24 hours. Allow the seeds to settle for 12 hours, and note the total volume occupied by the swollen seeds: the seeds of *Plantago psyllium* occupy a volume of not less than 14 mL, those of *Plantago ovata* not less than 10 mL, and those of *Plantago indica* not less than 8 mL.

TOTAL ASH <561>: not more than 4.0% of total ash.

ACID-INSOLUBLE ASH <561>: not more than 1.0% of acid-insoluble ash.

FOREIGN ORGANIC MATTER <561>: not more than 0.50%.

USP Monograph

2P33700
PSYLLIUM HUSK

>> **Psyllium Husk** is the cleaned, dried seed coat (epidermis) separated by winnowing and thrashing from the seeds of *Plantago ovata* Forskal, known in commerce as **Blond Psyllium** or **Indian Psyllium** or **Ispaghula**, or from *Plantago psyllium* Linne or from *Plantago indica* Linne (*Plantago arenaria* Waldstein et Kitaibel) known in commerce as **Spanish** or **French Psyllium** (Fam. Plantaginaceae), in whole or in powdered form.

PACKAGING AND STORAGE -- Preserve in well-closed containers, secured against insect attack (see Preservation under Vegetable and Animal Drugs in the General Notices).

BOTANIC CHARACTERISTICS --

Histology -- **Husk** -- The epidermis is composed of large cells having transparent walls filled with mucilage, and the cells swell rapidly in aqueous mounts and appear polygonal to slightly rounded in a surface view, when viewed from above (from below they appear elongated to rectangular). The swelling takes place mainly in the radial direction. The mucilage of the epidermal cells stains red with ruthenium red and lead acetate TS. The very occasional starch granules that are present in some of the epidermal cells, and that may be found embedded in the mucilage, are small and simple or compounded with four or more components.

Powdered Psyllium Seed Husk -- It is a pale to medium buff-colored powder, having a slight pinkish tinge and a weak characteristic odor. Occasional single and 2- to 4-compound starch granules, the individual grains being spheroidal plane to angular convex from 2 to 10 μ m in diameter, are found embedded in the mucilage. Entire or broken epidermal cells are filled with mucilage. In surface view, the epidermal cells appear polygonal to slightly rounded. Mucilage stains red with ruthenium red and lead acetate TS. Some of the elongated and rectangular cells representing the lower part of epidermis and also radially swollen epidermal cells can be found.

IDENTIFICATION --

A: Mounted in cresol -- Cells, viewed microscopically, are composed of polygonal prismatic cells having 4 to 6 straight or slightly wavy walls.

B: Mounted in alcohol and irrigated with water -- Viewed microscopically, the mucilage in the outer part of the epidermal cells swells rapidly and goes into solution.

MICROBIAL LIMITS <61> -- The total combined molds and yeasts count does not exceed 1000 per g, and it meets the requirements of the test for absence of *Salmonella* species and *Escherichia coli*.

TOTAL ASH <561>: not more than 4.0%.

ACID-INSOLUBLE ASH <561>: not more than 1.0%.

WATER, Method II <921>: not more than 12.0%.

LIGHT EXTRANEOUS MATTER -- [NOTE -- Perform this test in a well-ventilated hood.] Transfer 15.0 g to a 250-mL separator. Add about 90 mL of a liquid mixture of carbon tetrachloride and ethylene

dichloride (about 2:1), having a specific gravity of 1.45. Shake for 30 seconds, and allow to settle for 30 seconds. Repeat the shaking and settling twice more. Drain all the material and liquid except the floating layer. Add 25 mL of the liquid mixture, stir carefully, allow to settle, and drain as before. Repeat the washing of the floating layer

twice more, but use only 10 mL of the liquid mixture each time.

Transfer

the washed floating layer to a tared beaker, heat on a steam bath until the odor of the liquid no longer persists, dry at 40 degrees for 3 hours, allow to cool in a desiccator, and weigh: the limit is 15%.

HEAVY EXTRANEIOUS MATTER -- [NOTE -- Perform this test in a well-ventilated hood.] Transfer 10.0 g to a 250-mL separator. Add about 80 mL of carbon tetrachloride, and shake for 1 minute. Allow to stand for 5 minutes. Drain into a tared 1000-mL beaker the nonmucilaginous material that sinks to the bottom, taking care not to drain any of the floating material. Heat in a hot air oven, at a temperature not exceeding 90 degrees, until the odor of the liquid no longer persists, allow to cool in a desiccator, and weigh: the limit is 1.1%.

INSECT INFESTATION -- Transfer 25 g to a 250-mL beaker, add sufficient solvent hexane to saturate, add an additional 75 to 100 mL of solvent hexane, and allow to stand for 10 minutes, stirring occasionally with a stirring rod. Wet a sheet of filter paper with alcohol, and filter the mixture with the aid of vacuum. Discard the filtrate. Transfer the residue to the original beaker with the aid of alcohol. Add alcohol to bring the volume to 150 mL above the level of the transferred residue. Boil for 10 minutes. Filter through alcohol-wetted paper as above. Prepare a trap flask, consisting of a 2000-mL graduated, narrow-mouth conical flask into which is inserted a rubber disk supported on a stiff metal rod about 4 mm in diameter and longer than the height of the flask, the rod being threaded at the lower end and furnished with nuts and washers to hold the disk in place, and the disk being of the proper shape and size to prevent liquid in the body of the flask from spilling when it is pressed up against the neck from the inside. Transfer the residue to the trap flask, completing the transfer with the aid of hot water. Add sufficient hot water to bring the volume to 1000 mL. Add 20 mL of hydrochloric acid. Raise the rod, and support it so that the rubber disk is held above the liquid level. Rinse the rubber disk with hot water. Spray the inside of the neck of the flask with an antifoam spray. Boil for 30 minutes, and cool to room temperature. Add 40 mL of solvent hexane, and agitate for 1 minute by tilting the flask and

moving

the rod vertically with wrist action. Allow to stand for 5 minutes. Add water to bring the level of liquid to the neck of the flask, and allow to stand for 20 minutes. Simultaneously rotate the disk to free it from settled material, and raise it as far as possible into the neck of the flask. Prepare a sheet of ruled filter paper, with lines approximately

5

mm apart for filtration by moistening it with water and placing it on a vacuum funnel. Transfer the material trapped in the neck of the flask to

the filter with the aid of water. If necessary, wash the paper with alcohol to remove traces of hexane. Place the paper on a 100-mm petri dish that has been wetted with a solution containing equal volumes of glycerin and alcohol. Add 35 mL of solvent hexane to the flask, and gently stir with the trapping rod. Add water to bring the liquid level into the neck of the flask. Allow to stand for 15 minutes. Using the same technique as before, transfer the trapped material onto a separate paper. Examine the papers at 30X magnification: in the case of powdered

Psyllium Husk, not more than 400 insect fragments, including mites and psocids, can be seen; in the case of whole **Psyllium Husk**, not more than 100 insect fragments, including mites and psocids, can be seen.

SWELL VOLUME -- Transfer 250 mL of simulated intestinal fluid TS without enzymes to a glass-stoppered, 500-mL graduated cylinder. Gradually, with shaking, add 3.5 g of the **Psyllium Husk** until a uniform, smooth suspension is obtained. Dilute with the same fluid to 500 mL. Shake the cylinder for about 1 minute every 30 minutes for 8 hours. Allow the gel to settle for 16 hours (total time 24 hours). Determine the volume of the gel: it is not less than 40 mL per g for powdered **Psyllium Husk**, and not less than 35 mL per g for whole **Psyllium Husk**.

Attachment 2

USP monograph for psyllium (hemicellulose), published PF Vol. 30

BRIEFING

Psyllium Hemicellulose. Because there is no existing *USP* monograph for this article, a new monograph is being proposed.

(DSB: G. Giancaspro) RTS—40087-1

Add the following:

▲Psyllium Hemicellulose

» Psyllium Hemicellulose is the alkali soluble fraction of the husk from *Plantago ovata* Forssk. It consists of a combination of highly substituted arabinoxylan polysaccharides. These polysaccharides are linear chains of xylose units (β -(1→4)-xylan) to which are attached single units of arabinose and additional xylose. Rhamnose, galactose, glucose, and rhamnosyluronic acid residues are also present as minor constituents. It contains not less than 75.0 percent of dietary soluble fiber, calculated on the dried basis.

Packaging and storage— Preserve in tight containers. Store at 25°, excursions permitted between 15° and 30°.

Identification—

A: The powdered mucilage stains red with ruthenium red TS and lead acetate TS.

B: It meets the requirements of the test for *Swell volume*.

Total acidity— To a beaker, transfer 40 mL of the supernatant as obtained below in the test for *Swell volume* without disturbing the gel. Add 1 mL of phenolphthalein TS, and titrate with 0.03 N sodium hydroxide. Not more than 1.8 mL is consumed.

Microbial limits <61>— The total aerobic microbial count does not exceed 10^3 per g and the total combined molds and yeasts count does not exceed 10^2 per g. It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

Loss on drying <731>— Dry at 105° for 3 hours: it loses not more than 12.0% of its weight.

Total ash <561 >: not more than 5.0%.

Acid-insoluble ash <561>: not more than 1.0%.

Limit of alcohol—

Internal standard solution— Transfer 5.0 mL of *n*-propyl alcohol into a 500-mL volumetric flask containing approximately 450 mL of water. Dilute with water to volume, insert the stopper into the flask, and mix well.

Standard stock solution— Transfer 5.0 mL of absolute alcohol at $20 \pm 2^\circ$ into a 500-mL volumetric flask containing approximately 450 mL of water. Dilute with water to volume, insert the stopper into the flask, and mix well.

Standard solution— Transfer 10.0 mL of the *Standard stock solution* and 10.0 mL of *Internal standard solution* into a 100-mL volumetric flask. Dilute with water to volume, insert the stopper into the flask, and mix well.

Test solution— Transfer 0.5 g of Psyllium Hemicellulose, accurately weighed, into a 150-mL conical flask. Add about 90 mL of water, insert the stopper into the flask, and stir rapidly for 3 hours using a magnetic stirrer. Add 10.0 mL of the *Internal standard solution*, and mix well. Pass the sample through a filter having a 0.45- μm porosity.

Chromatographic system (see Chromatography <621>)— The gas chromatograph is equipped with a flame-ionization detector and a 0.53-mm \times 30-m fused silica analytical column coated with 3.0- μm G43 stationary phase. A 0.53-mm \times 2-m fused silica guard column may be used. The chromatograph is programmed as follows. Initially, the column temperature is equilibrated at 40° for 5 minutes. The temperature is then increased at a rate of 10° per minute to 230° , and is maintained at 230° for 3 minutes. The injection port temperature is maintained at 250° , and the detector is maintained at 300° . The carrier gas is helium. The split flow ratio is about 10:1, and the flow rate is maintained at about 4.0 mL per minute. Inject the *Standard solution*, and record the peak responses as directed for *Procedure*: the relative standard deviation for replicate injections is not more than 2%.

Procedure— Separately inject equal volumes (about 0.5 μL) of the *Standard solution* and the *Test solution* into the chromatograph, record the chromatograms, and measure the responses for all the peaks. Calculate the percentage of alcohol in the portion of Psyllium Hemicellulose taken by the formula:

$$1000(C/W)(R_U / R_S),$$

in which *C* is the concentration, in mg per mL, of alcohol in the *Standard stock solution*; *W* is the weight, in mg, of Psyllium Hemicellulose taken; and *R_U* and *R_S* are the ratios of the peak responses of alcohol to those of *n*-propyl alcohol from the *Test solution* and the *Standard solution*, respectively: not more than 12.0% (w/w) is found.

Organic volatile impurities, Method IV <467>: meets the requirements.

Heavy metals, Method II <231>: 10 μg per g.

Swell volume— Add 0.50 g of Psyllium Hemicellulose to a glass-stoppered, 100-mL graduated mixing cylinder. To avoid material clumping, hold the cylinder at a 45° angle, and gently rotate it while using a wash bottle to forcefully add about 30 mL of water. Add water to

bring the total volume to 100 mL, and cap the cylinder. Invert the cylinder several times until a uniform suspension is achieved, and allow to stand. Gently invert the cylinder several times again at 4 hours and 8 hours after the initial sample preparation, and allow to stand. Allow the gel to settle for 16 hours. Determine the volume of the gel: not less than 80 mL per g of Psyllium Hemicellulose is found.

Content of soluble dietary fiber—

Alcohol solution — Transfer 82.0 mL of alcohol to a 100-mL volumetric flask, dilute with water to volume, and mix.

Buffer solution— Dissolve 1.95 g of 2-(*N*-morpholino)-ethanesulfonic acid and 1.22 g of tris (hydroxymethyl)aminomethane in 170 mL of water. Adjust with 6 N sodium hydroxide to a pH of 8.2, dilute with water to 200 mL, and mix. [NOTE—It is important to adjust the pH to 8.2 at 24°. If the *Buffer solution* temperature is 20°, adjust the pH to 8.3; if the temperature is 28°, adjust the pH to 8.1. For deviations between 20° and 28°, adjust by interpolation.]

Acid solution— Prepare 0.561 N hydrochloric acid by dissolving 9.35 mL of 6 N hydrochloric acid in 70 mL of water. Dilute with water to 100.0 mL, and mix.

Phosphate buffer— Prepare a pH 6.0 phosphate buffer (see *Buffer Solutions* under *Reagents, Indicators, and Solutions*).

Protease solution— Dissolve 5 mg of protease in 0.1 mL of *Phosphate buffer*.

Enzyme purity— To ensure the absence of undesirable enzymatic activities and the presence of desirable enzymatic activities, proceed as directed for *Test preparations* and *Procedure* using the substrates listed in the following table in place of Psyllium Hemicellulose.

Substrate	Weight in g	Activity Tested
Pectin	0.2	Pectinase
Arabinogalactan	0.2	Hemicellulase
β-Glucan	0.2	β-Glucanase
Wheat starch	1.0	α-Amylase and amyloglucosidase
Corn starch	1.0	α-Amylase and amyloglucosidase
Casein	0.3	Protease

The enzyme preparation is suitable if more than 90% of the original weight of pectin, arabinogalactan, and β-glucan is recovered; not more than 2% of the original weight of casein and corn starch is recovered; and not more than 1% of the original weight of wheat starch is recovered. [NOTE—Test the enzyme purity of every new lot of enzyme and at 6-

month intervals thereafter.]

Blank preparations— Using two 400-mL tall-form beakers, appropriately labeled, proceed as directed for *Procedure* without Psyllium Hemicellulose.

Test preparations— Weigh accurately, in duplicate, approximately 0.2 g of Psyllium Hemicellulose, previously milled to very fine powder. [NOTE—Duplicates should differ by less than 1 mg in weight.] Transfer duplicate samples to appropriately labeled 400-mL, tall-form beakers, and proceed as directed for *Procedure*.

Procedure— Treat each preparation in the following manner. Add 40 mL of *Buffer solution* to the beaker. [NOTE—For the *Test preparation*, stir until Psyllium Hemicellulose is completely dispersed.] Add 125 μ L of heat-stable α -amylase solution, and stir to ensure uniform mixing. Cover the beaker with aluminum foil, and incubate over a water bath maintained at 95° to 100° for 15 minutes, with continuous agitation. [NOTE—Start timing once the water bath temperature reaches 95°; a total time of 35 minutes is usually sufficient.] Remove the beaker from the water bath, and cool to 60°. Remove the aluminum foil, scrape any ring from inside the beaker, and disperse any gels in the bottom of the beaker with a spatula. Rinse the walls of the beaker and the spatula with 10 mL of water, collecting the rinsings in the beaker. Add 500 μ L of *Protease solution*. Cover with aluminum foil, and incubate over a water bath maintained at 60 \pm 3° for 30 minutes with continuous agitation. [NOTE—Start timing when the bath temperature reaches 60°.] Remove the foil, and transfer 5 mL of *Acid solution* while stirring. Adjust, if necessary, with 1 N sodium hydroxide or 1 N hydrochloric acid to a pH of 4.28 \pm 0.07 at 60°. [NOTE—It is important to adjust the pH to 4.28 while the solution in the beaker is maintained at 60°, otherwise the pH will increase at lower temperatures.] Add 150 μ L of amyloglucosidase solution with stirring. Cover with aluminum foil, and incubate over a water bath maintained at 60 \pm 3° for 30 minutes with constant agitation. [NOTE—Start timing once the water bath reaches 60°.] Transfer approximately 40 mL of the beaker contents to a 50-mL centrifuge tube, and sonicate the tube contents for 3 minutes. Centrifuge at 10,000–14,000 rpm for 10 minutes. Carefully pour the supernatant into an appropriately labeled 600-mL tared beaker. Do not disturb any pellet in the bottom of the centrifuge tube. Add the remaining sample from the original 400-mL beaker into the centrifuge tube still containing the pellet. Rinse the 400-mL beaker with 15–20 mL of water, and add the rinsing to the 50-mL centrifuge tube. Centrifuge the sample at 10,000–14,000 rpm for 10 minutes. Carefully pour the supernatant into the 600-mL beaker containing the first supernatant. Add 390 mL (measured before heating) of alcohol at 60° to the 600-mL beaker. Cover the beaker, and allow to stand for at least 1 hour to form a precipitate.

Place 3 g of chromatographic siliceous earth into a clean air-dried crucible with a fritted disk. Heat the crucible containing chromatographic siliceous earth at 525° in a muffle furnace for at

least 4 hours. Cool. Pass deionized water through the crucible while applying constant suction. Rinse with acetone, and allow to air-dry. Store the crucible in a convection oven at approximately 130° for at least 2 hours before use. Weigh the prepared crucible to 0.1 mg before use. Wet the chromatographic siliceous earth in the crucible using a stream of *Alcohol solution* from a washing bottle, and apply suction to evenly distribute the chromatographic siliceous earth over the fritted disk. Maintaining the suction, transfer the supernatant and precipitate from the beaker to the crucible, and filter. Transfer any solid residue in the beaker with the aid of *Alcohol solution*. [NOTE—In some cases, gums may form during filtration, trapping liquid in the residue. If so, break the surface film with a spatula to improve filtration.] Wash the residue in the crucible sequentially with 30 mL of *Alcohol solution*, 20 mL of alcohol, and 20 mL of acetone. Dry the crucible containing the residue at 100° in a convection oven for at least 4 hours, cool to room temperature in a desiccator.

Determine the weight of the residue (*R*).

Use one of the duplicate residues from the *Test preparations* and one of the blank residues from the *Blank preparations* to determine the protein content, in mg, by placing the residue in a 500-mL Kjeldahl flask, and proceeding as directed for *Method I* under *Nitrogen Determination* (461). The protein content is determined by multiplying the content of nitrogen found by 6.25. Incinerate the residue from the remaining duplicate of the *Test preparation* and the *Blank preparation* as directed for *Total Ash* under *Articles of Botanical Origin* (561) at a reduced temperature of 525°, and determine the ash content as directed. Calculate the corrected average weight of the blank, in mg, *B*, by the formula:

$$R_B - P_B - A_B,$$

in which *R_B* is the weight, in mg, of the average blank residue for duplicate blank determinations; *P_B* is the content, in mg, of protein found in the blank; and *A_B* is the content, in mg, of ash found in the blank. Calculate the content of soluble dietary fiber, in percentage, by the formula:

$$100(R_U - P_U - A_U - B)/W_U,$$

in which *R_U* is the the weight, in mg, of average residue for the duplicate *Test preparations*; *P_U* is the content of protein, in mg, found in the Psyllium Hemicellulose; *A_U* is the content of ash, in mg, found in the Psyllium Hemicellulose; *B* is the average weight of the blank as calculated above; and *W_U* is the average weight, in mg, of the Psyllium Hemicellulose taken.

▲USP28

* A suitable sonicator is Sonifier 250 (or equivalent), equipped with a 12-mm tip, from Branson Ultrasonic Corp., Danbury, CT, in which an output control value of 3 and a cycle time of 75% generates a power output of 43 W.

Auxiliary Information— *Staff Liaison* : Gabriel I. Giancaspro, Ph.D., Senior Scientist and Latin American Specialist

Expert Committee : (DSB) Dietary Supplements: Botanicals

Phone Number : 1-301-816-8343

Attachment 3

FDA response to submission to Docket No. 78N-036L (Comment No. CP22, March 28, 1996) from P&G; Citizen Petition requesting the agency to include a drug-interaction precautionary statement for all laxatives



DEPARTMENT OF HEALTH & HUMAN SERVICES

HFA-305
Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV - 6 2000

4 0 8 0 '00 NOV -9 P12:07

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, Procter & 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

78N-036L

LET184

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.)

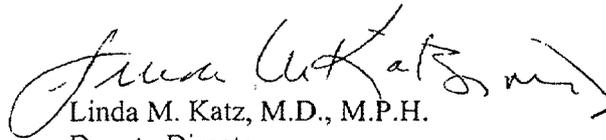
We have also considered the precautionary statements regarding drug-laxative interactions in current drug information compendia and on the labels of laxative drug products marketed in countries in support of the recommended labeling proposal. Based on all the data reviewed, we believe that a precautionary 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 inquiries in triplicate, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

Sincerely yours,

A handwritten signature in cursive script, appearing to read "Linda M. Katz".

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

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: NOV - 3 2000

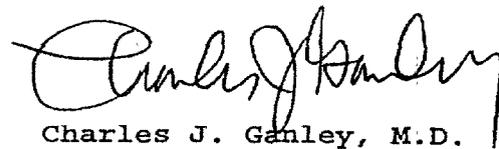
FROM: Director
Division of OTC Drug Products, HFD-560

SUBJECT: Material for Docket No. 78N-036L

TO: Dockets Management Branch, HFA-305

The attached material should be placed on public display under the above referenced Docket No.

This material should be cross-referenced to Comment No. CP22


Charles J. Ganley, M.D.

Attachment

Attachment 4

FDA response to submission to Docket No. 78N-036L (Comment No. C144, November 23, 1992) from Nonprescription Drug Manufacturers Association (NDMA)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

JUN 10 1993

Food and Drug Administration
Rockville MD 20857

R. William Soller, Ph.D.
Senior Vice President and
Director of Science & Technology
Nonprescription Drug Manufacturers Association
1150 Connecticut Avenue, NW
Washington, DC 20036

Re: Docket No. 78N-036L
Comments No. C144, LET58,
LET54, SUP7

Dear Dr. Soller:

This letter is in response to the Nonprescription Drug Manufacturers Association's (NDMA) submission dated November 23, 1992, concerning your research protocols designed to obtain information on physician and consumer understanding of various terms pertaining to the statement of identity (SOI) of OTC laxative drug products containing fiber. These products are included in the OTC drug review as bulk-forming laxative drug products. Your submission is filed as comment No. C144 under Docket No. 78N-036L in the Dockets Management Branch.

In my letter to you dated July 30, 1992 (LET58), I stated that the two protocols included in your May 1, 1992 (LET54) and June 1, 1992 (SUP7) submissions would not provide sufficient data to support a change in the SOI for bulk-forming laxative drug products. The November 23, 1992 submission contains revisions to these two protocols. You have stated that the revised protocols are designed to determine the attitudes and perceptions of physicians and consumers relating to the following three proposed statements of identity: 1. "Fiber Therapy for Irregularity (regularity was changed to irregularity);" 2. "Bulk-forming Laxative;" and 3. "Fiber Laxative." The revised protocols are also designed to determine consumer and physician perception and understanding of specific warning language in the labeling of fiber-containing OTC drug products. You stated that the agency made no mention of this latter issue in my July 30, 1992 letter.

The Office of OTC Drug Evaluation has reviewed your latest submission and concludes that the protocols will not provide sufficient data to support a change in the statement of identity for bulk-forming laxative drug products to "Fiber therapy for irregularity." We reach this conclusion for the following reasons:

First, the protocols do not address the concerns expressed in my July 30, 1992 letter regarding consumer understanding of "irregularity". In that letter, we questioned whether relief of

occasional constipation and avoidance of irregularity are medically synonymous. For relief or avoidance of "irregularity," long term therapy is suggested. Therefore, unless the clinical studies that support the claim for relief of occasional constipation (short term use) could also be found adequate to support the claim for relief or avoidance of irregularity (long term use), separate clinical trials would be needed to support the irregularity claim. Second, we are not aware of clinical studies that would adequately support a long-term indication.

Even if surveys were to be conducted, the proposed protocols have a number of problems, as discussed below:

1. There is some concern whether the consumer panel will adequately represent "ordinary" consumers. The protocol needs to include a method whereby a "representative" sample of consumers is obtained to participate in the study. Considering what is known about "volunteering biases," people who participate in these panels are not "ordinary".
2. The consumer study protocol does not directly measure what it purports to measure, i.e., consumer understanding of certain terms related to laxatives. The consumer study asks how easy or difficult the selected test terms are to understand, how descriptive the terms are of the products shown, and how much consumers agree or disagree that such products can be described by these terms. The decision regarding the appropriateness of the statement of identity is based on three terms. This narrow list of terms does not provide a test of the "best" possible terms to describe the proper use of the product. No terms will be tested that would more clearly communicate the intended use of these products to consumers nor does the study directly measure if consumers correctly understand the terms. Rather it measures respondents' attitudes about their own understanding of the term. How do consumers know whether or not they "understand" if a phrase is correct or incorrect? There is good research evidence that consumers have little knowledge of how well or poorly they understand a concept. A more direct method to measure consumer understanding would be to ask consumers to "check off" statements that describe how the product should or should not be used. This method may also detect whether different terms connote different usage patterns (e.g., long term vs. short term use).

3. The questions purported to deal with consumer and physician perception and understanding of specific label warning language relate more to consumers' ability to read than on "understanding".
4. The protocols should include, a priori, a set of criteria for interpreting the data. No information is given as to how the data will be analyzed and what criteria will be used to determine if a term or phrase is acceptable or unacceptable, misleading or nonmisleading.
5. The rationale for the physician survey is not clear. How would physicians know if a consumer would understand the terms being tested (question 5 on the physician questionnaire)? The questions in the physician survey will not provide direct information about physicians' views of how consumers would actually use these products. The questions ask physicians if they have any "concerns" about use of the products. Physicians may believe that these products are so safe that there could not be any safety problems, whether or not the products are misused. A more direct set of questions, measuring how products with different statement of identities would be used, would be a better measure of physicians' views.
6. Both the physician and the consumer protocols call for a mail panel. The rationale for the mail panel is not clear, particularly in light of NDMA's comments in a letter to FDA on September 18, 1991 regarding a similar proposed study on consumers' knowledge, attitudes, and beliefs about claims and warnings. In that letter, James Cope of NDMA opposed the use of mail panels. Mr. Cope stated the following:

"This type of panel consists of those who are willing to participate in testing and they are kept in a data base and utilized for testing of ads, products, concepts, and the like. The recruiting of mail panel consumers is a strenuous one in which only about 4% of the total population agrees to participate."

NDMA further stated in a letter to FDA on April 20, 1992:

"We [NDMA] propose [that FDA] . . . limit the study to Phase I of the latest protocol, eliminating the

Phase II mail panel portion. For reasons we discussed on March 26, 1992, we feel the mail panel is an inadequate approach to the issue of compliance with warnings."

7. The protocols do not address how the home setting will affect consumers' responses to the survey questions. The proposed consumer questionnaire specifically asks participants questions about a label that they are reading which has been mailed to them at home. NDMA's September 18, 1991 letter further stated,

"The assessment of labels in an 'unnatural' setting could be different than taking [the] product either in the home or at a store shelf. The proposed study under FTC 0274-91 is by mail and respondents are at home. There is little control over whom they speak to or what they read. In addition, it could be hypothesized that those who typically have used a product over a long period of time would not be consistently reading the labels. But those who are new to a brand of OTC medicine would in fact take the time to read the warning label. It is not clear that this has been worked into the design."

8. The consumer protocol, but not the physician protocol, included a power analysis. Information is needed on how the sample size of 200 physicians was determined and a description of the power of the sample.
9. We believe that, in a consumer study of level of comprehension and attention to warning labels, a 20% level of imprecision is inappropriate. The level of imprecision should be 10% or less.

Based on the information contained in your submission, the Office of OTC Drug Evaluation concludes that the data generated from implementation of the proposed protocols would not provide sufficient evidence to change the statement of identity of bulk forming laxatives to "Fiber therapy for Irregularity." The term "Fiber therapy for irregularity" implies that the drug corrects, avoids, or prevents irregularity; in our view, such claims would require the submission of clinical studies. Terms such as "Bulk-

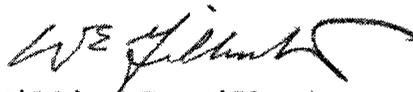
forming laxative" or "Fiber laxative" when used as statements of identity would not require such clinical proof because these terms do not imply prevention or long term correction of disease.

Further, certain regulations must be considered in determining the statement of identity. Under the regulations in 21 CFR 201.61, the statement of identity of an OTC drug is limited to the established name of the drug, if any, followed by an accurate statement of the general pharmacological category(ies) of the drug or the principal intended action(s) of the drug. The established name of the drug is defined in section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352(e)(3)). The recognized pharmacological category for a drug used to relieve constipation is "laxative." Because of the many classes of laxatives, and for the sake of clarification, a term describing the class to which a particular laxative drug belongs is also included in the monograph. Based on the regulations in 21 CFR 201.61 and the tentative final monograph, an example of a statement of identity for a product containing bran for the relief of constipation would be "bran" followed by the term "bulk forming laxative," i.e., the established name of the drug and its pharmacological category. Wherever possible, the agency prefers to use the general pharmacologic category as the statement of identity because information on the principal intended action is provided in the indications. However, we might consider including the term "fiber laxative" as an optional (allowable) indication for bulk-forming laxatives in the final monograph as follows: "Fiber therapy for relief of occasional constipation" [which may be followed by "(irregularity)"].

Any comment you may wish to make on the above information should be submitted in three copies, identified with the docket and comment numbers shown at the beginning of this letter, to the Dockets Management Branch (HFA-305), Food and Administration, Room 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

We hope this information will be helpful.

Sincerely yours,



William E. Gilbertson, Pharm. D.
Director
Monograph Review Staff
Office of OTC Drug Evaluation
Center for Drug Evaluation and Research

Attachment 5

Submission to Docket No. 78N-036L (November 26, 1986) from P&G, regarding directions for use of bulk-forming laxatives



THE PROCTER & GAMBLE COMPANY

SHARON WOODS TECHNICAL CENTER

November 26, 1986

11511 REED HARTMAN HIGHWAY CINCINNATI, OHIO 4524

Dockets Management Branch (HFA-305)
Food and Drug Administration
Room 4-62
5600 Fishers Lane
Rockville, Maryland 20857

1986 NOV 28 AM 10 10

Re: Docket No. 78N-036L
Laxative Drug Products for Over-the-Counter Human Use;
Tentative Final Monograph. Notice of Proposed Rulemaking:
51 Federal Register 35136 (October 1, 1986).

Ladies and Gentlemen:

The Procter & Gamble Company ("Procter & Gamble") submits these comments to the above-referenced proposed rulemaking to amend the tentative final monograph (TFM) for OTC laxative drug products. As a manufacturer and distributor of over-the-counter drug products, including bulk-forming laxatives, Procter & Gamble is directly affected by this proposal.

Procter & Gamble supports the Agency's objective for this proposed rulemaking which, in effect, corrects the directions for use of bulk-forming laxatives previously proposed in the Laxative TFM (50 FR 2154). The Agency's previous position that bulk-forming laxatives must only be taken "in a single daily dose" was contrary to current medical practice for routine use of these products, it significantly deviated from the directions for use on labels of marketed products, and it posed a safety risk of esophageal obstruction if maximum levels were administered in a single dose.

As was stated in the preamble to this proposed rulemaking, the Agency seeks, through this proposal, to provide sufficient flexibility to manufacturers to accommodate the various dosages of marketed bulk laxative products that have to been shown to be safe and effective. With this objective in mind, Procter & Gamble requests that the Agency consider the following comments pertaining to this proposal:

1. Clarify the Proposed Monograph Wording To Specifically Provide for Both Single and Divided Doses of Bulk-forming Laxatives

A strict interpretation of the wording in proposed 21 CFR 334.52 may lead one to conclude that only multiple dosing of bulk-forming laxatives is permitted, to the exclusion of single daily dosing. The revised monograph wording now uses the term "in divided doses" in the directions for use. Current wording in the proposed rulemaking is stated (generically) as:

"Oral dosage is up to ___ grams daily in divided doses of ___ to ___ grams per dose."

1021-03/1

We define "divided" as meaning "separated into two or more parts." Therefore, according to our definition, the proposed monograph wording of divided doses suggests that the product must be taken in two or more doses. Although we believe the Agency's intent in this proposal is to specifically provide for both single and multiple daily doses, the proposed monograph wording does not explicitly state this provision.

To ensure that the amended TFM provides for both single and multiple dose regimens, Procter & Gamble requests clarification of the wording in proposed 21 CFR 334.52. The following wording is suggested:

"Oral dosage is up to ___ grams daily, administered as ___ to ___ grams per dose either as a single daily dose or as divided ___ doses."

This revised wording clearly establishes that both single and multiple doses are permitted in the monograph. Moreover, the proposed wording maintains the Agency's new limitation on the the amount of active that can be taken in a single dose. This maximum single dose limitation minimizes the risk for the rare occurrence of esophageal obstruction which may occur if the maximum total daily dose is administered as a single dose.

The newly added provision of divided daily doses gives consumers the flexibility needed to tailor dose regimens to their individual needs. Of equal importance, however, is the provision for single daily dosing since label directions of several bulk-forming laxative products expressly state directions for use as one or more doses per day. Depending on an individual's response to bulk-forming laxatives, single daily dosing at a submaximal level may provide an appropriate level of effectiveness, compliance, and convenience to a portion of laxative users.

2. Reassess the Dose Ranges Specified for All Bulk-Forming Laxatives

The proposed rulemaking now establishes dose ranges for divided daily doses of bulk-forming laxatives. Although it would be reasonable to calculate the ranges for divided daily doses using the effective total daily dose ranges specified for each active ingredient in the TFM, it does not appear that these divided dose ranges were established on that basis.

In particular, we note inconsistencies in this proposal pertaining to the minimum doses specified for the divided dose ranges of actives. For psyllium products, the newly established minimum divided dose (2.5 grams) specified in this proposed rule corresponds to the minimum effective daily dose specified in the TFM. For all other actives, however, the newly established minimum divided doses do not correspond to the minimum effective daily doses specified in the TFM. The following table illustrates this point:

Comparison of Dose Ranges Cited
in TFM and in this Proposed Rule

<u>Active</u>	<u>Effective Total Daily Dose Range Cited in TFM (Grams/Day)</u>		<u>Divided Dose Range Cited in this Proposal (Grams/Dose)</u>	
	<u>Minimum</u>	<u>Maximum</u>	<u>Minimum</u>	<u>Maximum</u>
	Bran	6	14	1
Methylcellulose, etc.	4	6	0.45	3
Karaya	5	10	3.5	7
Malt soup extract	12	64	3	32
Polycarbophil	4	6	1	1
Psyllium	2.5	30	2.5	7.5

The minimum divided doses specified for all active ingredients except psyllium are below the established minimum effective total daily dose cited in the TFM. For some actives such as bran and methylcellulose, the minimum divided dose is approximately one-sixth to one-tenth of the TFM's minimum effective total daily dose. Whether these actives are administered as a single dose or in multiple doses, the potential clearly exists that all actives, except for psyllium, could be administered at subtherapeutic dose levels. For example, according to the table above, directions on bran products could specify dosing for five times a day with 1 gram/dose, without even reaching the minimum effective total daily dose required for a laxation benefit (6 grams/day).

Procter & Gamble requests that the Agency reassess the method by which the minimum divided doses were determined in this proposed rule and consider the possible consequences if monograph conditions are established for dose levels that have not been shown to be effective. We submit that the method used to derive the minimum divided dose for psyllium products ought to be equally applied to all other active ingredients.

3. Delete the Psyllium Total Daily Dose Limitation

Procter & Gamble goes on record to support the previous objections filed on June 14, 1985, by Paul M. Hyman of Hyman, Phelps and McNamara, P.C., on behalf of Searle Pharmaceuticals Inc. and Rydelle Laboratories, Inc., and on June 13, 1985, by The Proprietary Association, which pertain to the total daily dose limitation placed on psyllium products. In spite of these previous objections, the Agency in this proposal continues to place a total daily dose limitation on psyllium.

Furthermore, whereas the Agency previously specified in the TFM that there is no maximum daily dose limit for bran (50 FR 2154), the proposed rule does not carry this same exemption for bran (51 FR 35137). Placing daily dose limitations on either bran or psyllium is contrary to the Laxative Panel's recommendation that "it is unnecessary to impose a specific daily dosage limitation at this time" for either bran or psyllium products (40 FR 12906 and 12908).

We believe it is imprudent to restrict the intake of dietary fiber from any source in the context of total dietary management goals. Mr. Hyman's June 14, 1985, submission to the Agency provides scientific evidence that a limitation on the daily intake of dietary fiber would be ill-advised in view of the recognized health benefits provided by an adequate daily intake of fiber.

It is recognized that the Agency must establish appropriate labeling conditions for psyllium and bran in the OTC laxative monograph, and in doing so, it must specify effective dose ranges for that ingredient. For psyllium, the effective daily dose range is 2.5 to 30 grams; for bran, the effective daily dose range is 6 to 14 grams. These ranges establish the amount of bran or psyllium needed in a day to obtain a laxation effect. However, effective daily dose ranges of fiber products should not be equated to a maximum level of total daily intake. The effective dose ranges for laxation should not be used to limit the intake of fiber for those people who, because of inadequate food sources of dietary fiber or for other needs, may require additional fiber in their diet. Thus, the monograph should be written without the implied language suggesting limitations on psyllium or bran use, and we recommend the directions for use be amended to correct the implied limitation.

For psyllium products, we request the directions for use in proposed 21 CFR 334.52(d)(7) be amended to the following:

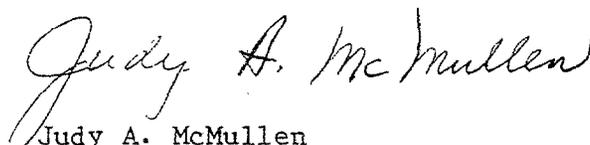
(7) For products containing any psyllium ingredient identified in Section 334.10(f). Adults and children 12 years of age and over: Oral dosage is up to 30 grams daily, administered as 2.5 to 7.5 grams per dose either as a single daily dose or as divided doses. There is no maximum daily dose (emphasis added). Children 6 to under 12 years of age: Up to 15 grams daily in single or divided doses of 2.5 to 3.75 grams per dose. Children under 6 years of age: Consult a doctor.

This language is the same as the Agency had previously provided for bran products in the Laxative TFM (50 FR 2154).

Procter & Gamble gratefully acknowledges the Agency's response to industry's request to amend the directions for use previously specified in the Laxative TFM. We trust that the comments provided in this submission will assist you in establishing safe and effective monograph conditions for bulk-forming laxative products.

Sincerely,

THE PROCTER & GAMBLE COMPANY
Health and Personal Care Division



Judy A. McMullen
Professional and Regulatory Services