

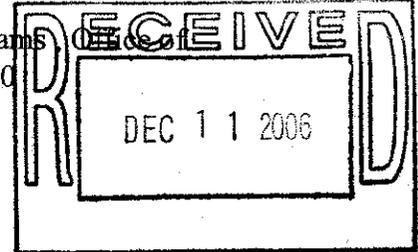
Memorandum

Date: DEC 8 2006

From: Consumer Safety Officer, Division of Dietary Supplement Programs, Office of
Nutritional Products, Labeling and Dietary Supplements, HFS-810

Subject: 75-Day Premarket Notification of New Dietary Ingredients

To: Dockets Management Branch, HFA-305



Subject of the Notification: "psyllium hemicellulose"

Firm: The Proctor and Gamble Company

Date Received by FDA: August 16, 2006

90-Day Date: November 14, 2006

In accordance with the requirements of section 413(a) of the Federal Food, Drug, and Cosmetic Act, the attached 75-day premarket notification and related correspondence for the aforementioned substance should be placed on public display in docket number 95S-0316 as soon possible since it is past the 90-day date. Thank you for your assistance.

Theresa Prigmore

1995S-0316

RPT 366



Nadia N. St. Luce, Ph.D.
US Regulatory Affairs, Personal Health Care
The Procter and Gamble Company
Health Care Research Center
8700 Mason-Montgomery Road
Mason, Ohio 45040-9462

NOV 21 2006

Dear Dr. St. Luce:

This is to inform you that the notification you submitted, dated August 14, 2006, pursuant to 21 U.S.C. 350b(a)(2)(section 413(a)(2) of the Federal Food, Drug, and Cosmetic Act (the Act)) was filed by the Food and Drug Administration (FDA) on August 16, 2006. Additional information was received on October 17 and 27, 2006. Your notification concerns the substance called psyllium hemicellulose, *Plantago ovata* Forssk., that you intend to market as a new dietary ingredient.

According to your notice the conditions for use for psyllium hemicellulose are the following:
"The recommended daily intake will be 2.5 grams of psyllium hemicellulose powder in 8 ounces of water to be taken up to three times per day. This will result in a maximum intake of psyllium hemicellulose of 7.5g/day. The product will be labeled that it is not intended or recommended for use by children under 6 unless provided under physician's guidance." Directions: "One heaping TEASPOON in 8 ounces of water up to three times daily. Under 6 years: Consult a doctor. NOTICE: Mix this product with at least 8 oz (a full glass) of water. Taking without sufficient liquid may cause choking. Do not take if you have difficulty swallowing."

Under 21 U.S.C. 350b(a), the manufacturer or distributor of a dietary supplement containing a new dietary ingredient that has not been present in the food supply as an article used for food in a form in which the food has not been chemically altered must submit to FDA, at least 75 days before the dietary ingredient is introduced or delivered for introduction into interstate commerce, information that is the basis on which the manufacturer or distributor has concluded that a dietary supplement containing such new dietary ingredient will reasonably be expected to be safe. FDA reviews this information to determine whether it provides an adequate basis for such a conclusion. Under section 350b(a)(2), there must be a history of use or other evidence of safety establishing that the new dietary ingredient, when used under the conditions recommended

or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe. If this requirement is not met, the dietary supplement is considered to be adulterated under 21U.S.C. 342(f)(1)(B) because there is inadequate information to provide reasonable assurance that the new dietary ingredient does not present a significant or unreasonable risk of illness or injury.

In accordance with 21 CFR 190.6(c), FDA must acknowledge its receipt of a notification for a new dietary ingredient. For 75 days after the filing date, your client must not introduce or deliver for introduction into interstate commerce any dietary supplement that contains the new dietary ingredient that is the subject of this notification.

Please note that acceptance of this notification for filing is a procedural matter, and thus, does not constitute a finding by FDA that the new dietary ingredient or supplement that contains the new dietary ingredient is safe or is not adulterated under 21 U.S.C. 342. FDA is not precluded from taking action in the future against any dietary supplement containing your new dietary ingredient if it is found to be unsafe, adulterated, or misbranded.

Your notification will be kept confidential for 90 days after the filing date of August 16, 2006. After the 90-day date, the notification will be placed on public display at FDA's Division of Docket Management in docket number 95S-0316. Prior to that date, you may wish to identify in writing specifically what information you believe is proprietary, trade secret or otherwise confidential for FDA's consideration.

If you have any further questions concerning this matter, please contact Theresa Prigmore at (301) 436-1446.

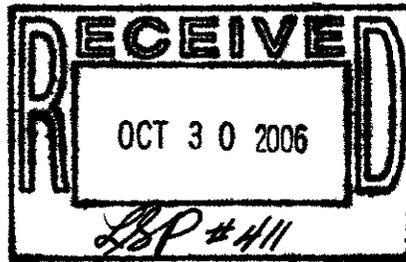
Sincerely yours,



Linda S. Pellicore, Ph.D.
Supervisory Team Leader, Senior Toxicologist
Division of Dietary Supplement Programs
Office of Nutritional Products, Labeling
and Dietary Supplements,
Center for Food Safety and Applied Nutrition



The Procter & Gamble Company
Mason Business Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462
www.pg.com



October 30, 2006

ATTN: Dr. Linda Pellicore

Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820)
Center for Food Safety and Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835
FAX- (301) 436-2636

Re: New Dietary Ingredient (NDI) Notification for Psyllium Hemicellulose- Followup Question

Dear Ms. Pellicore:

This letter is to follow up on the October 28th, 2006 telephone call between FDA-CFSAN and P&G (to me). Responding directly to the FDA's question raised in that call, we herein submit additional information to FDA to support the 75-day pre-market notification for marketing Psyllium Hemicellulose as a new dietary ingredient. Enclosed with this original letter are two identical copies.

We hope this letter is fully responsive to FDA's information needs. Should you have any questions regarding this notification, please contact me at (513) 622-1672, or Dr. Nadia St. Luce at 513-622-5566, FAX 513-622-0558, or e-mail: stluce.nn@pg.com.

Sincerely,

THE PROCTER & GAMBLE COMPANY

Maury Bandurraga, Ph.D.
US Regulatory Affairs, Personal Health Care



Question from FDA:

How many grams of psyllium hemicellulose (PHC) are in one average heaping teaspoon of our new Metamucil product (containing PHC) when mixed in 8 oz. water, and what is the variation expected since commercial teaspoons vary a little in size?

P&G Response:

There are 2.5 +/- 0.2 grams of the new dietary ingredient PHC in one heaping teaspoon of our new Metamucil product (containing PHC) mixed in 8 oz of water, with a relative standard deviation of 8%.

Calculation Basis:

There are 7.2 +/- 0.5 grams of our new Metamucil product (containing PHC) in one heaping teaspoon of our new Metamucil product (containing PHC) mixed in 8oz of water. This represents a relative standard deviation of 7%, and was based on multiple measurements of heaping teaspoons purchased at US department stores.

The balance of our new Metamucil formulation (containing PHC) is comprised of maltodextrin, sucrose, starch, flavors and colors, all approved for their intended food use.



NDI 411

The Procter & Gamble Company
Mason Business Center
8700 Mason-Montgomery Road
Mason, OH 45040-9462
www.pg.com

October 17, 2006

ATTN: Vicki Lutwak

Office of Nutritional Products, Labeling and Dietary Supplements (HFS-820)
Center for Food Safety and Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835

Re: New Dietary Ingredient (NDI) Notification for Psyllium Hemicellulose

Dear Ms. Lutwak:

This letter is to follow up on the October 11th, 2006 conference call between FDA-CFSAN and P&G. Responding directly to the FDA's questions raised in that call, we herein submit additional information to FDA to support the 75-day pre-market notification for marketing Psyllium Hemicellulose as a new dietary ingredient. Enclosed with this original letter are two identical copies.

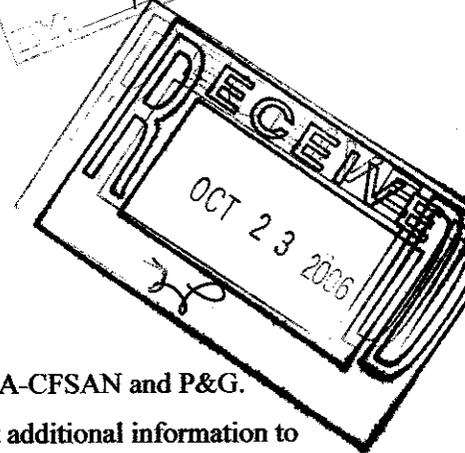
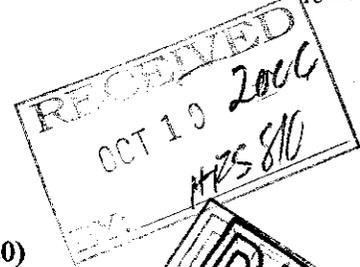
We hope this letter is fully responsive to FDA's information needs. Should you have any questions regarding this notification, please contact me at 513-622-5566, FAX 513-622-0558, or e-mail: stluce.nn@pg.com.

Sincerely,

THE PROCTER & GAMBLE COMPANY

Nadia N. St. Luce, Ph.D.

US Regulatory Affairs, Personal Health Care





Question 1 from FDA:

How many grams of psyllium hemicellulose (PHC) are in one heaping teaspoon of Metamucil when mixed in 8 oz. water?

P&G Response:

There are 2.7 grams of PHC in one heaping teaspoon of Metamucil mixed in 8oz of water.

Calculations

Metamucil Powder, e.g., Smooth Texture Sugar-Free, contains 3.4 grams psyllium husk per one heaping teaspoon (single adult dose).

The PHC content of psyllium husk averages 80% by weight.

The amount of PHC in 3.4 grams of psyllium husk is: $3.4\text{g} (0.8) = 2.72\text{ g PHC}$

Question 2 from FDA:

What are the calculation steps that show how we compare the Swell Volume of PHC in product to the Swell Volume PHC in Metamucil (psyllium husk (PSH))?

P&G response:

P&G uses the technical measure referred to as “swell volume” to characterize dietary fibers. Swell Volume measurement is a 16 hour process performed by USP method.

The swell volume of psyllium husk is 62 ml/1.0 grams (NDI document: p. 22, Table 9). The standard dose of Metamucil contains 3.4 grams psyllium husk per dose. The swell volume of 3.4 grams of psyllium husk in one dose of Metamucil is:

$3.4\text{ g} \times 62\text{ ml}/1.0\text{ g} = 210.8\text{ ml}$, Swell Volume of gel from psyllium husk in one dose of Metamucil

The swell volume of PHC is 104 ml/1.0 grams (NDI document: p. 22, Table 9). The recommended adult dose of PHC in product is 2.5 gram. The swell volume of a 2.5 gram dose of PHC in product is:

$2.5\text{ g} \times 104\text{ ml}/1.0\text{ g} = 260\text{ ml}$ swell volume per dose from PHC

Question 3 from FDA:

What are the reasons why the increase in swell volume does not pose a concern in relation to choking?

P&G Response:

The following information demonstrates why the increase in PHC Swell Volume doesn't pose a choking concern.

Swell Volume is calculated based on the amount of water bound 16 hours after the water is added to the product (USP method). Due to the extended period of time used in the method, the swell volume is not a good indicator of a fiber products choking hazard as most consumers consume the product within 20



minutes of dissolution in water. The slow rate of gelation, reduced thickness of gel formed and gel rheology of the PHC product as compared to the psyllium husk (PSH) are all factors that leading to a reduction of the potential choking hazard. Keeping in mind the typical consumer habit of mixing and then immediately consuming a fiber beverage, a PHC product would be less thick and easier to swallow than one containing psyllium husk and thus would actually pose less of a choking hazard. Additionally, consumer tests conducted with PHC product shows that there have been no issues with swallowing. Experimental data to support the reduced gel density and longer time to gel of PHC vs. psyllium husk are presented below.

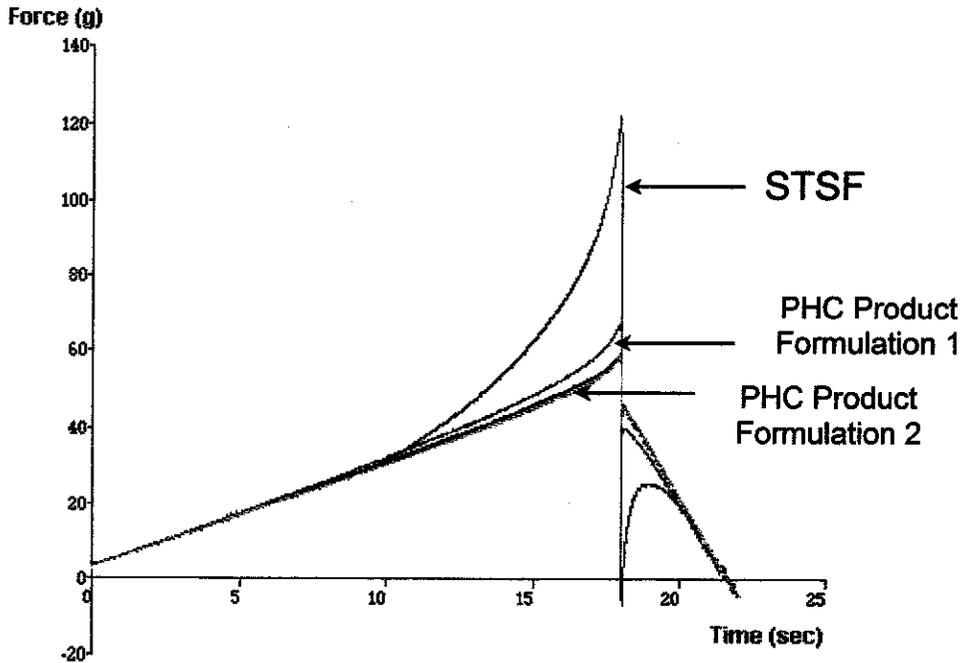
Gel Density/Thickness

The gel formed from PHC is less dense and less viscous when compared to PSH and thus decreases the potential of a choking hazard. One adult dose of Metamucil (3.4 g of psyllium husk (PSH)) contains 2.7 g of PHC. A 2.5 g dose of PHC (260 ml) yields a 23% increase in swell volume at 16 hrs, compared with the swell volume from a 3.4 g dose of PSH (210.8 ml). The reason the extracted PHC exhibits a larger swell volume is that the removal of cellulose frees up binding sites on PHC that bind and hold a greater quantity of water than the PHC in psyllium husk, which is still bound to cellulose. This 23% increase in swell volume is due to the greater amount of water in the PHC gel, resulting in gel formation that is less dense. It is well established that the choking hazard is significantly reduced as density decreases.

As a comparative measure of the relative ease of swallowing at a typical time of consumption, a Standard Sieve Test (P&G Method HCK D19) was used. In this test, a full adult dose of Metamucil is stirred into 8 oz. of water and left to stand for 20 minutes. The solution is poured through a pre-weighed 40 mesh sieve. The sieve is re-weighed and the increase in weight is a measure of the amount of gel left on the sieve. This test gave a value of 125.1 -128.2 g for two samples when performed on Metamucil Smooth Texture Sugar-Free Orange. When the same test was performed on a PHC product, the weight of gel on the sieve was 62.4-68.6 g. A larger amount of material passing through the sieve (i.e., less residual on the sieve) is an indication of less viscous/less dense material. This demonstrates that although the PHC has more swell volume per gram, the resulting gel is significantly less dense and less viscous at the typical time of consumption, thus reducing any potential choking hazard. This test also reflects the consumer drinking habits as most consumers drink Metamucil within the first 20 minutes of suspending the particles in water.

Graph 1 below illustrates the results of another study which shows that when a probe was added to a mixed drink of PHC product and to mixed Metamucil Smooth Texture Sugar Free (STSF) product, more force was needed after about 12 seconds to move the probe to the bottom of the container with the Metamucil product compared to the PHC product. The lower viscosity of the gel formed at typical consumption time greatly reduces the choking hazard potential of PHC.

Graph 1: Metamucil STSF vs. PHC Product Thickness



Common viscosity measurement techniques do not provide meaningful data when applied to PSH and PHC colloid suspensions. The data generated here were designed to relate to the actual consumer experience.

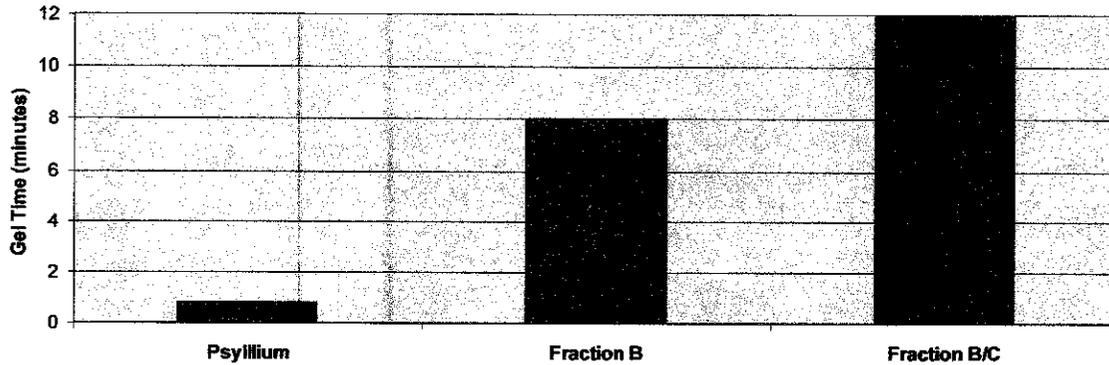
Gel Formation Timing

Graph 1 above also demonstrates that the psyllium husk gel forms faster than the gel for PHC. Two additional studies are provided to show that gel formation takes longer for PHC and that the gel formed is less dense as compared to Metamucil. Graph 2 below, shows the time required for gel formation of psyllium husk and PHC. These data demonstrate that it takes longer for gel formation with PHC (12 minutes) than with psyllium husk (1 minute). This test was conducted by a visual method.

Another test was performed to show the length of time PHC takes to thicken and gel compared to psyllium husk. In this test, either psyllium husk or PHC was dissolved in a beaker of water at room temperature, equipped with a magnetic spin bar set at a standard spin rate. The time required for the mixture to thicken sufficiently to stop the spin bar was measured. For psyllium husk this took less than a minute, for PHC this took over 40 minutes. Based on the fact that the gel formation takes much longer to occur with PHC (fraction B/C) compared to psyllium husk, the viscosity of PHC is less at time of consumption and therefore would not pose a choking hazard.

Graph 2: Gelation of Psyllium vs. PHC

Rate of gelation in restricted water environment: Longer time to gel results in less oesophageal blockage potential.



In conclusion, P&G has determined that although PHC has an increased swell volume compared to psyllium husk in Metamucil, this does not represent a choking hazard. This can be confirmed by the data presented which demonstrates that: 1) the PHC gel at the time of swell volume measurement (16 hrs) is less dense, 2) PHC gel forms at a slower rate vs. PSH resulting in a less viscous product at the time of consumption.

Question 4 from FDA:

Provide Certificate of Analysis for the commercial product containing PHC.

P&G Response:

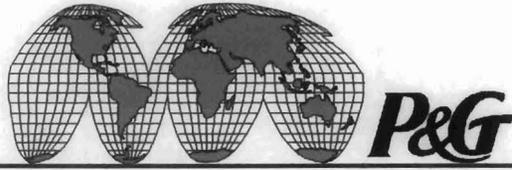
Certificates of Analysis for several lots of PHC tested against USP standard are attached.

Question 5 from FDA:

Provide Method of analysis for PHC.

P&G Response:

The analysis method used for PHC is attached.

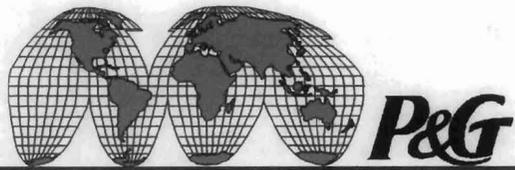


CERTIFICATE OF ANALYSIS

PRODUCT: Psyllium Hemicellulose

TESTING DATE: August 14, 2005

LOT#	BPR-66-1153		
TESTING	SPECIFICATION	Lot Average	Method
Identification A	Stains red with ruthenium red	Pass	USP
Identification B	Meets requirements for Swell Volume	Pass	USP
Loss On Drying (%)	< 12%	6.64	USP
Swell Volume (ml/0.5g)	> 40ml	56.58	USP
Ethanol (%)	< 12%	6.11	USP
TAMC (cfu/g)	< 1000 cfu/g	83.3	USP
Yeast/Mold (cfu/g)	<100 cfu/g	<25	USP
Coliforms (cfu/g)	Negative	Negative	USP
E.Coli	Negative	Negative	USP
Salmonella	Negative	Negative	USP
S.Auereus	Negative	Negative	USP
Appearance	Pass / Fail	Pass	USP
Odor	Pass / Fail	Pass	USP
Total Acidity (ml)	NMT 1.8ml	<0.1	USP
Soluble Dietary Fiber	NLT 75%	85.1	USP
Organic Volatile Impurities	Meets Spec	Yes	USP
Heavy Metals	NMT 10µg/g	<10	USP
Total Ash (%)	NMT 5 %	2.5	USP
Acid Insoluble Ash (%)	NMT 1 %	0.25	USP



CERTIFICATE OF ANALYSIS

PRODUCT: Psyllium Hemicellulose

TESTING DATE: August 14, 2005

LOT#	BPR-66-1152		
TESTING	SPECIFICATION	Lot Average	Method
Identification A	Stains red with ruthenium red	Pass	USP
Identification B	Meets requirements for Swell Volume	Pass	USP
Loss On Drying (%)	< 12%	8.46	USP
Swell Volume (ml/0.5g)	> 40ml	53.8	USP
Ethanol (%)	< 12%	7.8	USP
TAMC (cfu/g)	< 1000 cfu/g	66.7	USP
Yeast/Mold (cfu/g)	<100 cfu/g	25	USP
Coliforms (cfu/g)	Negative	Negative	USP
E.Coli	Negative	Negative	USP
Salmonella	Negative	Negative	USP
S.Auereus	Negative	Negative	USP
Appearance	Pass / Fail	Pass	USP
Odor	Pass / Fail	Pass	USP
Total Acidity (ml)	NMT 1.8ml	<0.05	USP
Soluble Dietary Fiber	NLT 75%	87.5	USP
Organic Volatile Impurities	Meets Spec	Yes	USP
Heavy Metals	NMT 10µg/g	<10	USP
Total Ash (%)	NMT 5 %	2.4	USP
Acid Insoluble Ash (%)	NMT 1 %	0.2	USP

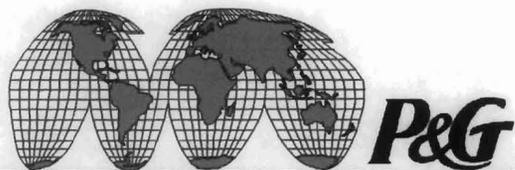


CERTIFICATE OF ANALYSIS

PRODUCT: Psyllium Hemicellulose

TESTING DATE: August 14, 2005

LOT#	BPR-66-1151		
TESTING	SPECIFICATION	Lot Average	Method
Identification A	Stains red with ruthenium red	Pass	USP
Identification B	Meets requirements for Swell Volume	Pass	USP
Loss On Drying (%)	< 12%	8.96	USP
Swell Volume (ml/0.5g)	> 40ml	54	USP
Ethanol (%)	< 12%	8.5	USP
TAMC (cfu/g)	< 1000 cfu/g	66.6	USP
Yeast/Mold (cfu/g)	<100 cfu/g	<25	USP
Coliforms (cfu/g)	Negative	Negative	USP
E.Coli	Negative	Negative	USP
Salmonella	Negative	Negative	USP
S.Auereus	Negative	Negative	USP
Appearance	Pass / Fail	Pass	USP
Odor	Pass / Fail	Pass	USP
Total Acidity (ml)	NMT 1.8ml	<0.05	USP
Soluble Dietary Fiber	NLT 75%	79.6	USP
Organic Volatile Impurities	Meets Spec	Yes	USP
Heavy Metals	NMT 10µg/g	<10	USP
Total Ash (%)	NMT 5 %	2.4	USP
Acid Insoluble Ash (%)	NMT 1 %	0.25	USP



CERTIFICATE OF ANALYSIS

PRODUCT: Psyllium Hemicellulose

TESTING DATE: August 14, 2005

LOT#	BPR-66-1150		
TESTING	SPECIFICATION	Lot Average	Method
Identification A	Stains red with ruthenium red	Pass	USP
Identification B	Meets requirements for Swell Volume	Pass	USP
Loss On Drying (%)	< 12%	8.0	USP
Swell Volume (ml/0.5g)	> 40ml	52.9	USP
Ethanol (%)	< 12%	6.9	USP
TAMC (cfu/g)	< 1000 cfu/g	100	USP
Yeast/Mold (cfu/g)	<100 cfu/g	<25	USP
Coliforms (cfu/g)	Negative	Negative	USP
E.Coli	Negative	Negative	USP
Salmonella	Negative	Negative	USP
S.Auereus	Negative	Negative	USP
Appearance	Pass / Fail	Pass	USP
Odor	Pass / Fail	Pass	USP
Total Acidity (ml)	NMT 1.8ml	<0.05	USP
Soluble Dietary Fiber	NLT 75%	81.4	USP
Organic Volatile Impurities	Meets Spec	Yes	USP
Heavy Metals	NMT 10µg/g	<10	USP
Total Ash (%)	NMT 5 %	2.6	USP
Acid Insoluble Ash (%)	NMT 1 %	0.17	USP

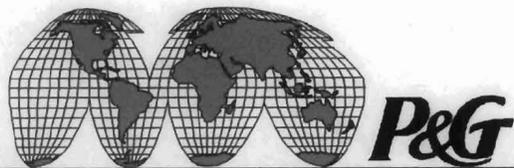


CERTIFICATE OF ANALYSIS

PRODUCT: Psyllium Hemicellulose

TESTING DATE: August 14, 2005

LOT#	BPR-66-1149		
TESTING	SPECIFICATION	Lot Average	Method
Identification A	Stains red with ruthenium red	Pass	USP
Identification B	Meets requirements for Swell Volume	Pass	USP
Loss On Drying (%)	< 12%	5.55	USP
Swell Volume (ml/0.5g)	> 40ml	52.63	USP
Ethanol (%)	< 12%	6.16	USP
TAMC (cfu/g)	< 1000 cfu/g	100	USP
Yeast/Mold (cfu/g)	<100 cfu/g	25	USP
Coliforms (cfu/g)	Negative	Negative	USP
E.Coli	Negative	Negative	USP
Salmonella	Negative	Negative	USP
S.Auereus	Negative	Negative	USP
Appearance	Pass / Fail	Pass	USP
Odor	Pass / Fail	Pass	USP
Total Acidity (ml)	NMT 1.8ml	<0.05	USP
Soluble Dietary Fiber	NLT 75%	95.2	USP
Organic Volatile Impurities	Meets Spec	Yes	USP
Heavy Metals	NMT 10µg/g	<10	USP
Total Ash (%)	NMT 5 %	2.4	USP
Acid Insoluble Ash (%)	NMT 1 %	0.12	USP



CERTIFICATE OF ANALYSIS

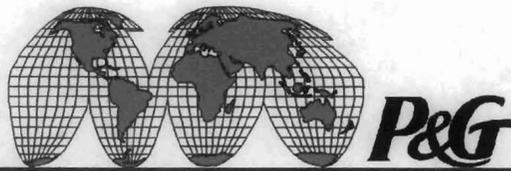
PRODUCT: Psyllium Hemicellulose

TESTING DATE: August 14, 2005

LOT#	BPR-66-1148		
TESTING	SPECIFICATION	Lot Average	Method
Identification A	Stains red with ruthenium red	Pass	USP
Identification B	Meets requirements for Swell Volume	Pass	USP
Loss On Drying (%)	< 12%	7.7	USP
Swell Volume (ml/0.5g)	> 40ml	52.6	USP
Ethanol (%)	< 12%	6.4	USP
TAMC (cfu/g)	< 1000 cfu/g	150	USP
Yeast/Mold (cfu/g)	<100 cfu/g	25	USP
Coliforms (cfu/g)	Negative	Negative	USP
E.Coli	Negative	Negative	USP
Salmonella	Negative	Negative	USP
S.Auereus	Negative	Negative	USP
Appearance	Pass / Fail	Pass	USP
Odor	Pass / Fail	Pass	USP
Total Acidity (ml)	NMT 1.8ml	<0.05	USP
Soluble Dietary Fiber	NLT 75%	77.40	USP
Organic Volatile Impurities	Meets Spec	Yes	USP
Heavy Metals	NMT 10µg/g	<10	USP
Total Ash (%)	NMT 5 %	2.70	USP
Acid Insoluble Ash (%)	NMT 1 %	0.14	USP

PREPARED BY : _____
 PRE-APPROVAL QA: _____
 APPROVED BY QA: _____

DATE: _____
 DATE: _____
 DATE: _____



CERTIFICATE OF ANALYSIS

PRODUCT: Psyllium Hemicellulose

TESTING DATE: August 14, 2005

LOT#	BPR-66-1147		
TESTING	SPECIFICATION	Lot Average	Method
Identification A	Stains red with ruthenium red	Pass	USP
Identification B	Meets requirements for Swell Volume	Pass	USP
Loss On Drying (%)	< 12%	7.1	USP
Swell Volume (ml/0.5g)	> 40ml	50.4	USP
Ethanol (%)	< 12%	6.18	USP
TAMC (cfu/g)	< 1000 cfu/g	366.6	USP
Yeast/Mold (cfu/g)	<100 cfu/g	75	USP
Coliforms (cfu/g)	Negative	Negative	USP
E.Coli	Negative	Negative	USP
Salmonella	Negative	Negative	USP
S.Auereus	Negative	Negative	USP
Appearance	Pass / Fail	Pass	USP
Odor	Pass / Fail	Pass	USP
Total Acidity (ml)	NMT 1.8ml	<0.05	USP
Soluble Dietary Fiber	NLT 75%	92.8	USP
Organic Volatile Impurities	Meets Spec	Yes	USP
Heavy Metals	NMT 10µg/g	<10	USP
Total Ash (%)	NMT 5 %	2.4	USP
Acid Insoluble Ash (%)	NMT 1 %	0.26	USP

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 \rightarrow 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 $\langle 61 \rangle$ —The total aerobic microbial count does not exceed 1000 cfu per g and the total combined molds and yeasts count does not exceed 100 cfu per g. It meets the requirements of the tests for absence of *Salmonella* species and *Escherichia coli*.

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

Total ash $\langle 561 \rangle$: not more than 5.0%.

Acid-insoluble ash $\langle 561 \rangle$: 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- μ m 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- μ m 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 μ L) 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 µL of *Protease solution*. Cover with aluminum foil, and incubate over a water bath maintained at 60 ± 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 ± 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 µL of amyloglucosidase solution while stirring. Cover with aluminum foil, and incubate over a water bath maintained at 60 ± 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:

$$100(R_v - P_v - A_v - B)/W_v,$$

in which R_v is the weight, in mg, of average residue for the duplicate *Test preparations*; P_v is the content of protein, in mg, found in the **Psyllium Hemicellulose**; A_v 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_v is the average weight, in mg, of the **Psyllium Hemicellulose** taken.

Residual solvents (467): meets the requirements.

(Official January 1, 2007)

* 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* : Maged H. Sharaf, Ph.D., Senior Scientist

Expert Committee : (DSB05) Dietary Supplements - Botanicals

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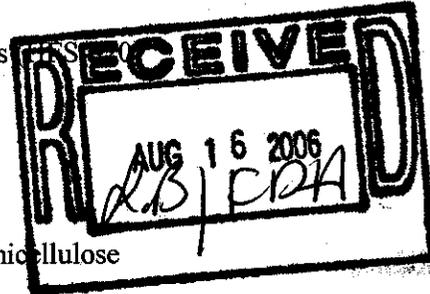
Phone Number : 1-301-816-8318



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August 14, 2006

Office of Nutritional Products, Labeling and Dietary Supplements
Center for Food Safety and Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740-3835



Re: New Dietary Ingredient (NDI) Notification for Psyllium Hemicellulose

Dear Sir/Madam:

In accordance with 21CFR §190.6, The Procter & Gamble Company (P&G) hereby notifies the Food and Drug Administration (FDA) of our intent to market psyllium hemicellulose (also known as PHC) as a fiber dietary supplement.

PHC is a soluble polysaccharide fiber extracted from psyllium seed husk (PSHusk) and comprises 80% of currently marketed psyllium fiber dietary supplements.

The recommended daily intake will be 2.5 grams PHC up to three times per day in powder or capsule form. Labeling will include information required for current psyllium dietary supplements. The product will be labeled as a psyllium fiber supplement.

This NDI notification describes a history of safe use of PSHusk (and hence PHC) and their compositional relationship, a review of the safety information on PSHusk and the expected exposure data, and other required elements as specified by FDA.

We are submitting an original set and two copies as required. We have provided copies of all the published and unpublished data relied on to make the determination of safety for dietary ingredient use. In addition, we have included a courtesy copy of a Confidential CD (with all information), for your convenience. We would be glad to make additional CD copies if helpful.

Following earlier discussions with FDA, we have clearly indicated which studies are pivotal to make the safety determination in the body of the notification, and which are supportive (located in Appendix A). We have also shown the level of PHC tested in each study, and relationship to the psyllium test substance, and comparison to the expected exposure level for dietary ingredient use. This information is provided in a summary table in the overall safety review section, and in tables heading individual safety reviews.

We have also provided company confidential information within the document which is clearly marked. This information should not be released to any other entity, person or company without the written permission of P&G.

Based on our intended dietary supplement use and labeling, this notification supports P&G's determination that PHC, a new dietary ingredient, is reasonably expected to be safe for its labeled use.



Should you have any questions regarding this notification, please contact Dr. Nadia St. Luce at 513-622-5566, FAX 513-622-0558, or e-mail: stluce.nn@pg.com.

Sincerely,

THE PROCTER & GAMBLE COMPANY

Nadia N. St. Luce, Ph.D.

US Regulatory Affairs, Personal Health Care

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NEW DIETARY INGREDIENT NOTIFICATION INFORMATION

Section I

A. Manufacturer

1. Address and Contact Information

Distributor of formulated dietary supplement

The Procter & Gamble Company
Health Care Research Center
8700 Mason Montgomery Road
Mason, Ohio 45040
Phone-513-622-5566

Contact

Nadia N. St. Luce, Ph.D., US Regulatory Affairs
Personal Health Care
Ph: 513-622-5566
Fx: 513-622-0558
e-mail: stluce.nn@pg.com

Manufacturer of Psyllium hemicellulose

P&G Phoenix Plant
2050 South 35th Ave.
Phoenix, AZ 85009

Section II

A. New Dietary Ingredient Name and Background on Relationship to Psyllium Seed Husk

The name of the new dietary ingredient is psyllium hemicellulose (PHC).

PHC is the main soluble fiber, gelling, polysaccharide component of psyllium seed husk (PSHusk), the major component of currently marketed Metamucil and other psyllium products. PSHusk is marketed as a daily dietary fiber supplement in addition to its approved use as bulk laxative under the OTC Laxative Tentative Final Monograph. To our knowledge, the extracted

and purified PHC dietary ingredient as described in this notification was not marketed in that form as a dietary supplement in the US prior to 1994. However, it is the major soluble fiber component of PSHusk, which was marketed and a part of the food supply prior to 1994 in the US.

PHC meets the definition of a dietary ingredient because it is a botanical extracted from PSHusk to provide a concentrated form of soluble fiber that we intend to market as powder (tubs or sachets) or capsules. The fiber powder will be used by consumers to increase fiber intake beyond their normal dietary intake, similar to currently marketed psyllium fiber supplements, by taking with water (capsule) or drinking after mixing with water (tubs or sachet). The powder will not be marketed as a conventional food ingredient or as a sole item of a meal or the diet, and will be labeled as a fiber dietary supplement. Therefore PHC meets the statutory definition of a dietary ingredient found in section 201(ff) of Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321).

Procter & Gamble (P&G) analytical data as well as data reviewed by FDA in the 1998 soluble fiber health claim for PSHusk support that PHC is a concentrated form of soluble fiber from PSHusk. On average, the soluble fiber content in PSHusk is about 67.6%. The soluble fiber content in PHC is about 84.5%. The calculated ratio of soluble fiber content ($67.6/84.5$), along with other analytical data presented in later sections, leads to the conclusion that PHC comprises 80% of PSHusk. Thus, on a wet weight basis, PHC makes up about 80% of the soluble fiber in PSHusk composition before extraction. After extraction, the concentration of soluble fiber in the extracted PHC raw material product is 85-95%, with the remainder being a significantly reduced level of protein and cellulosic insoluble fiber material.

PHC is the main polysaccharide component of PSHusk that forms a viscous gel upon mixing with water. Both PSHusk and PHC form this characteristic gel, characterized by “swell volume”, which increases with purity of the gelling polysaccharide PHC. PHC comprises the primary polysaccharide of PSHusk (80% by wet weight). Table 1 illustrates comparison of the

swell volume (gelling ability) and soluble fiber composition of PSHusk and PHC on a wet weight basis.

Table 1
Summary Comparison of PHC and PSHusk Content and Properties - % wet weight (See page 13, Table 6, for compositional data for PHC)

Raw Material	PHC content	Soluble Fiber content	Swell Volume (ml/0.5g)
Psyllium Husk	80	~70	31
PHC extracted from Psyllium Husk	100	~85 (77-95)	52

PHC is extracted from PSHusk under mild conditions to provide a concentrated form of the soluble fiber for dietary supplement use. Mild conditions use 0.2 N sodium hydroxide. Standard alkaline extractions using concentrations greater than 1.0 N sodium hydroxide were shown to degrade the polysaccharide. The extraction process will be described later and evidence is presented to show that the PHC polysaccharide structure is unchanged during the extraction process from PSHusk. Because PHC is not chemically modified after undergoing the extraction and separation process from PSHusk (supported by data in this submission), the safety data contained in this NDI that supports the safety of PSHusk also applies to PHC. This is based on the fact that the removed insoluble material during the extraction and separation process (cellulose and a small amount of protein) is assumed to be neutral with respect to toxicity, a conservative assumption.

The conclusion that the PHC will reasonably be expected to be safe for the intended use, to meet the DSHEA requirement of 201 ff(1) (21 USC 321(ff)(1)) is supported both qualitatively and quantitatively throughout this document. The safety conclusion is based on a history of safe use of PHC as the major polysaccharide component of PSHusk, and on a number of safety studies on psyllium ingredients which contained an average of 80% PHC. A total of 19 studies referred to in the main body of this document are considered pivotal to the safety determination of the NDI

substance and are summarized in Table 16, page 37 in Section IV. Two additional supportive studies were removed from the body of the previously submitted NDI document and are referenced in Section VII, Appendix B (page 77).

In addition to our determination in this document, PSHusk, which includes PHC, has been declared safe for consumption by FDA in their 1998 approval of the soluble fiber health claim (63 FR 8119 Feb. 18, 1998). It is the soluble fiber (PHC) from PSHusk that actually is the basis for the health claim.

The amount of PHC in the test material, comparison to intended exposure, and a summary of safety conclusions are presented at the beginning of every safety section. The summary table of all the pivotal studies with comparison of the ratio of the highest PHC test dose to intended PHC exposure is presented at the beginning of the overall safety section in Section IV, Table 16, page 37. This summary table contains each reference number and study type. The summary is followed by discussion of each of the toxicological areas examined.

In conclusion, as the major component of PSHusk, the toxicity data relevant to the husk applies to PHC. A number of analytical and physical chemical property comparisons and physiological studies will be presented later in this notification to explain the compositional similarities between extracted PHC and the soluble fiber in PSHusk. Additionally, data will be presented to demonstrate the safety of the isolated soluble fiber, PHC (NDI substance) utilizing existing safety studies on PSHusk (test substance).

As required in 21 CFR190.6(b)(2), the Latin binomial name (including author) of any herb or other botanical has been confirmed as provided in the National Center for Biotechnology Information located at <http://ncbi.nlm.nih.gov>. NCBI Entrez Taxonomy Database for *Plantago ovata* and is given in Table 2.

Table 2
Latin Binomial Name and Taxonomy

Latin Binomial Name:	Plantago ovata Forsk
Taxonomic Serial No.:	504438
Kingdom:	Plantae
Taxonomic Rank:	Species
Synonym(s):	Plantago brunnea Morris
	Plantago fastigiata Morris
	Plantago gooddingii A. Nels. & Kennedy
	Plantago insularis Eastw.
	Plantago insularis var. fastigiata (Morris) Jepson
	Plantago insularis var. scariosa (Morris) Jepson
	Plantago minima A. Cunningham
Common Name(s):	desert Indian wheat
Taxonomic Status:	
Current Standing:	accepted
Data Quality	
Indicators:	
Record Credibility Rating:	verified - standards met
Kingdom	Plantae -- Planta, plantes, plants, Vegetal
Subkingdom	Tracheobionta -- vascular plants
Division	Magnoliophyta -- angiospermes, angiosperms, flowering plants, phanérogames, plantes à fleurs, plantes à fruits
Class	Magnoliopsida -- dicots, dicotylédones, dicotyledons
Subclass	Asteridae
Order	Plantaginales
Family	Plantaginaceae -- plantains
Genus	Plantago L. – Indianwheat, plantain
Species	Plantago ovata Forsk. -- Desert Indianwheat
Geographic Division:	North America
Jurisdiction/Origin:	Continental US, Native

The Procter and Gamble Company (P&G) plans to manufacture this ingredient at their facility in Phoenix, AZ.

Details of the PHC ingredient, comparison to PSHusk (from which it is extracted), the extraction process, and data to support its safety follow.

B. Chemical Identification, Manufacture and Product Analysis

1. Chemical Name

Psyllium Hemicellulose (PHC)

2. Nomenclature

PHC is the active soluble fiber component in PSHusk products marketed as dietary fiber supplement and bulk laxative under the brand name Metamucil. PHC comprises 80% of PSHusk on a wet weight basis. PHC is extracted under mild alkaline conditions from PSHusk to remove insoluble fiber (cellulosic) and protein components. The PHC extracted has the same polysaccharide structure as the soluble fiber in PSHusk.

Upon extraction with mild alkali solution, PSHusk can be fractionated into 3 parts (Fractions A, B, and C) representing different types of fiber. Fraction A (~15% insoluble) is cellulosic, nongel-forming, insoluble fiber material which is unfermented (not broken down by bacteria in the gut). Fraction B, the major component of PSHusk (~65% soluble) consists of viscous, gel forming polysaccharides which are poorly fermented (not substantially broken down by bacteria in the gut). The last component of PSHusk, Fraction C (~20% soluble) is also a viscous gel-former; however it is rapidly fermented, in contrast to the other 2 fractions. The extracted soluble fiber fractions B and C total about 85% of PSHusk on a wet weight basis. The remainder of the material (A), the insoluble fraction, totals about 15% (cellulose, proteins).

Table 3
Comparison of PSHusk and PHC Fiber Composition and Properties on a wet weight basis
(PSHusk before extraction; PHC after extraction)

Composition	Psyllium seed husk PSHusk (% by weight)	Psyllium hemicellulose PHC (% by weight)	Main components	Amount of fermentation in human (Extent of bacterial breakdown in gut)
Insoluble Fraction A	~15-25	~5-15	Insoluble cellulosic fiber and protein, non-gel forming	Very low
Fraction B	~65-70	~70-75	Viscous, gel-forming	Low
Fraction C	~10-15	~15-20	Viscous, gel-forming	Rapid
Total BC PHC	~75-85 (average 80)	~85-95 (average 90)	Viscous, gel-forming	----

References: Fisher (2004), Marlett (2003), Oliver (2000), FR. No. 63, 2/19/1998.

Throughout its development history, PHC has been identified generically as either “Fraction B”, “Fraction BC” or “Marlett”, each derived by extraction from PSHusk under mild alkaline conditions to remove the insoluble “Fraction A” (cellulosic materials and protein). These generic descriptions are used in several of the source documents that appear in this review. As will be shown later (Section II, C2, page 19), chromatographic comparisons of elution peaks for PSHusk and PHC show that notified dietary ingredient PHC is enriched in Fractions BC and depleted in Fraction A compared to PSHusk.

Some of the reference documents also use the term “psyllium hydrophilic mucilloid” or “mucilage” to describe PSHusk or its main active component (PHC) because of the gelling and water holding capacity properties of the PHC. Psyllium gum is also used in some places to describe the gel-forming properties of PHC, such as in “psyllium husk gum”. The description of the source (or preparation) of the material in each reference allows determination whether the material being referenced as a gum is seed husk only (PSHusk), extracted hemicellulose (PHC), or the entire seed (seed gum).

For clarity, Table 4 below describes the terms typically used for psyllium and psyllium products with their common synonyms, their meanings, and their characteristic Swell Volume (by USP test specification). The lower Swell Volume of the seed gum vs. PSHusk or the husk extract (PHC) indicates a lower polysaccharide composition. Swell Volume of PSHusk and PHC is closely related to level of PHC measured in each, supporting the fact that the PHC structure doesn't change during the PHC dietary ingredient extraction process.

Table 4
Psyllium Terms and Definitions

Name	Synonyms Used	Definition	Fiber Composition (% Wet Weight)	Swell Volume* (mL/g)
Psyllium Seed Husk (PSHusk)	-psyllium fiber -psyllium husk -psyllium seed husk gum -psyllium hydrophilic mucilage	Outer layer of psyllium seed used commercially in Metamucil and other bulk laxative and dietary fiber supplement products.	~70% soluble fiber ~30% insolubles	40
Psyllium Hemicellulose	-PHC -Soluble fiber component of PSHusk -Psyllium seed husk mucilage soluble fiber -Marlett -PSHusk Fractions B and C -PSHusk Fraction B	Soluble fiber fractions B and C extracted from psyllium seed husk by mild alkali. B= poorly fermented polysaccharides (70-75% PHC) C= rapidly fermented polysaccharides (20-25% of PHC)	~85% soluble fiber ~15% insolubles	80
Ispagula husk	-psyllium husk -Psyllium seed husk	Mucilage (viscous gelling material) from <i>P. ovata</i> husks	~70% soluble fiber ~30% insolubles	40
Psyllium pectins	-Prepared psyllium mucilage	Methylated PSHusk to form viscous gels used as food thickeners	Methylated polysaccharides	30
psyllium seed gum	-Psyllium gum -Extracted psyllium seed	Hot water extract of psyllium seed	Polysaccharide broken down into smaller subunits	40
<i>Plantago</i>	-Blond Psyllium	Entire harvested seed	~70% soluble	20

5. Molecular Weight of PHC

Psyllium hemicellulose: 300,000-500,000 Daltons

For comparison- psyllium husk: 1.62×10^6 Daltons

“Molecular weight, tertiary structure, water binding and colon behavior of ispaghula husk fiber.”

(Phillip), Proceedings of the Nutrition Society (2003), 62: 211-216.

6. Botanical Family Name

Extract of *Plantago ovata*

7. Part of Plant Used

PHC is extracted from PSHusk.

8. Source

PHC is an extract of PSHusk and is compositionally identical to the soluble fiber contained in PSHusk. The primary commercial source for both PHC and PSHusk is *Plantago ovata* (*syn. Plantago ispaghula*) Class Plantaginaceae. In the literature, the term psyllium may also be used to refer to the ripe seeds or epidermis of this or other *Plantago* species. In this document, the term “psyllium seed” is used to describe the seeds, which are higher in protein content than the PSHusk used commercially or as a source of PHC.

Plantago ovata is also known in commerce as Blond Psyllium, Indian Psyllium or Ispaghula. Psyllium husk is the cleaned, dried seed coat (epidermis) separated by winnowing and thrashing from the seeds of *Plantago ovata*.

When PHC is extracted from PSHusk, the polysaccharide composition does not change; the process simply concentrates the PHC component from 80% up to 85 - 95% on a wet weight basis. PSHusk contains a high proportion of the desired hemicellulose composed of a xylan backbone linked with arabinose, rhamnose, and galacturonic acid units (arabinoxylans). The plant itself grows in India, Afghanistan, Iran, Israel, northern Africa, Spain and the Canary

Islands. The plant is also cultivated in India and neighboring countries, Arizona (US), and southern Brazil.

Table 5 below provides the monosaccharide content of polysaccharides contained in psyllium hemicellulose.

Table 5
Monosaccharide Content of Polysaccharides in PHC

Component	% W/W (Dry Basis)
Xylose	67
Arabinose	19
Uronic Acids	2
Rhamnose	1
Galactose	2
Glucose	1

Reference: US Patent # 6287609 (2001)

9. Manufacturing Process: Extraction of Psyllium Hemicellulose

5 PAGES TOTAL

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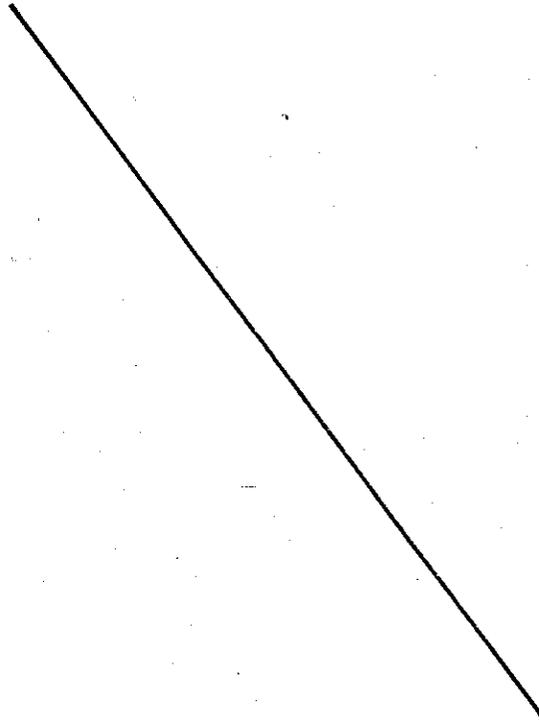
CONTAINS

TRADE SECRET

CONFIDENTIAL

COMMERICAL

INFORMATION



12. Stability of Psyllium Hemicellulose

Commercially, PHC will be packaged in appropriate HDPE bottles to ensure stability over the labeled shelf life of the product to maintain the soluble fiber functionality standards required by USP.

C. Comparison of Psyllium Seed Husk and Psyllium Hemicellulose

PHC is the major polysaccharide component of PSHusk as shown by analytical and performance comparisons of the two materials.

This section discusses the analytical and performance similarities and differences between PSHusk and PHC based on several endpoints, to demonstrate that PSHusk is made up of 80% PHC (the soluble fiber Fraction B or B/C) and 20% insolubles (Fraction A). Both analytical data and performance characteristics reflect the overlap in composition and the removal of the insoluble fraction from PSHusk via extraction to isolate and purify PHC. These comparative techniques include: physiological comparison, Size Exclusion Chromatography, Swell Volume, Rheology, Dewetting, Soluble Fiber Analysis, Fermentation, and Protein Analysis.

Net, these comparisons clearly show that the PHC produced by extraction and purification of PSHusk represents the soluble fiber component of PSHusk. In comparison to the PSHusk starting material, PHC contains less protein, less insolubles, more soluble fiber, more fermentation potential (due to lower insolubles), higher Swell Volume, increased viscosity, and greater dewetting capacity.

1. Relationship of Physiological and Predictive Physical Chemical Properties for Psyllium Components

Reviews (Schneeman, 2001; Fulgoni, 2001, Schneeman, 1994) on fiber chemistry, physiology, and the specific effect of psyllium fiber (PSHusk) upon laxation, stool-softening, cholesterol-lowering and post-prandial glycemic response take into account the water-holding, polymer swelling, and gel-forming capability of psyllium. For example, it is proposed in the reviews that the polysaccharides of psyllium bind water, increasing the stool mass, volume and lubricity, inducing peristalsis and thereby facilitating passage of the stool. It is hypothesized that cholesterol lowering occurs because the increased viscosity of the aqueous layer at the intestinal lumen prevents bile acids from being reabsorbed so that they are lost through the stool. Blood cholesterol is lowered because cholesterol is being used to synthesize bile acids to replace those lost. An increase in viscosity of the fluids at the boundary of the intestinal lumen also delays absorption of sugars, thereby attenuating glycemic response.

Below, the analytical characterization of PHC and PSHusk, is followed by several *in vitro* measures of polymer swelling (Swell Volume), water-holding (de-wetting), and gel-forming (rheology), where the values for PSHusk and PHC are compared. The data show the overlap of

the soluble fiber component (PHC) with PSHusk, demonstrating that PHC is a major component of PSHusk. The data also provide information about the characteristics of PSHusk and PHC fractions A, B, and C (where B and C are the soluble fiber), with molecular weight, solubility, water holding capacity, and other differences which reflect their physiological roles in the body.

2. Characterization of Psyllium Hemicellulose and Psyllium Seed Husk by Size-Exclusion Chromatography with Multi-Angle Light Scattering and Refractive Index Detection

2 PAGES TOTAL

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3. Swell Volume

Comparison of PHC and PSHusk Swell Volume (Water Holding Capacity) demonstrates that PHC has less insoluble non-polysaccharide material after PSHusk extraction.

Swell Volume is a measurement related to the gel-forming, swelling (WHC or Water Holding Capacity) of the polymer (polysaccharide). Table 9 below compares the Swell Volume of 95% PSHusk USP (1) before sanitization and (2) after sanitization to PHC after pasteurization.

**Table 9
Water Holding Capacity of PHC vs. PSHusk**

Psyllium Form	Measured Swell Volume (mL/0.5 g)*	Swell Volume (mL/g – calculated from Measurement)**	Swell Volume USP Requirement (mL/g)
(1) 95% Psyllium Seed Husk preSanitization	31	62	40
(2) 95% Psyllium Seed Husk postSanitization	27	54	40
(3) Psyllium Hemicellulose postPasteurization	52	104	80

*P&G express Swell Volume in mL/.5g, while USP expresses it in mL/g.

**Column illustrates P&G Swell Volume when expressed in mL/g in comparison with USP.

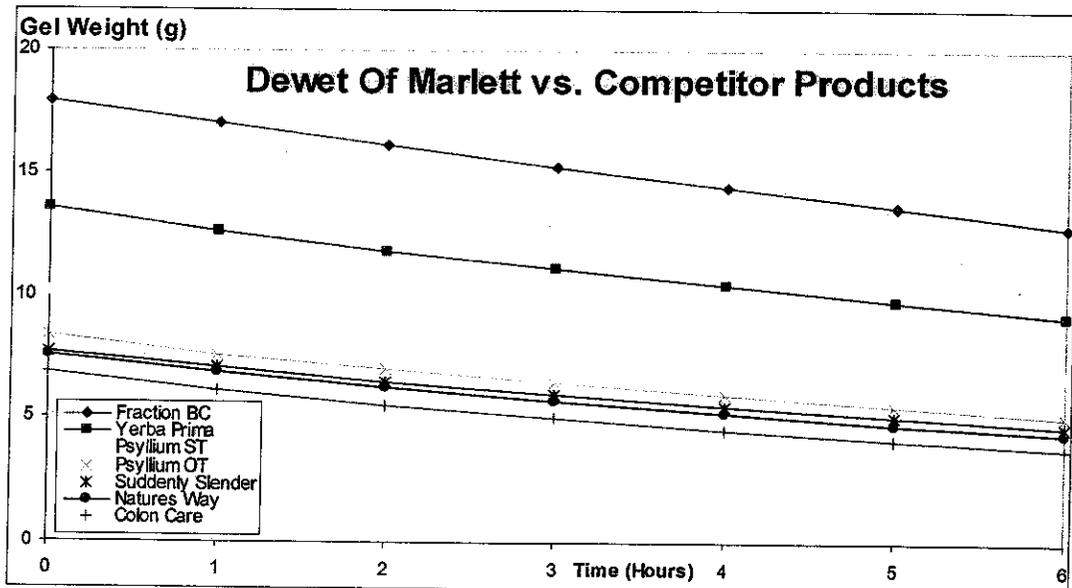
These data reflect a very slight decrease in Swell Volume due to sanitization of (PSHusk), and in both cases the results exceed the USP requirement. In addition, PHC has a greatly enhanced

Swell Volume compared with PSHusk because non-swelling components (cellulose, lignin, lipids, and proteins) have been removed and hydrogen-bonding sites between cellulose and hemicellulose have been freed by the removal of cellulose, thereby increasing the availability of water-binding sites on the hemicellulose. In addition, the slightly more mild conditions of pasteurization of the PHC material compared with PSHusk steam sanitization, also likely contribute to maintenance of a high Water Holding Capacity as shown by the Swell Volume test.

4. Dewetting of Psyllium Hemicellulose vs. Psyllium Seed Husk

The dewetting test demonstrates removal of insolubles from PSHusk to extract the soluble fiber PHC because the higher concentration of soluble fiber provides more sites available to pick up and strongly hold on to water. In this test, the PHC sample (Fraction BC) is referred to as Marlett which is the original patented technology for extracting and fractionating PHC from PSHusk. This product (Fraction BC) was compared to 2 commercial products containing PSHusk (referred to as ST (smooth texture)) and OT (original texture) as well as to several similar competitors' PSHusk products. In each case, the sample (0.15g) under test is allowed to swell in water as in the Swell Volume test. After complete swelling, the supernatant liquid is removed and the gelled portion is sealed in dialysis membrane tubing. The sample is then hung in an oven at 37⁰C and weighed at hourly intervals. The results from these evaluations are presented in the graph below.

Graph # 1



These data indicate that PHC (Fraction BC above) has a higher gel weight initially, and retains more weight than does PSHusk (Psyllium Smooth Texture (ST) and Psyllium Original Texture (OT)). This is once more consistent with the idea that more sites are available to hold water on PHC than on PSHusk due to removal of the insoluble fraction from PSHusk.

5. Rheology

In Table 10 below, Yield Stress (Pa) values are displayed for psyllium seed husk (milled) and PHC at 0.5, 1.5 and 3.0% w/w concentrations.

**Table 10
Yield Stress (Pa)**

Sample	0.5 %	1.5%	3.0%
Psyllium Seed Husk	1.27	5.34	15.94
Psyllium Hemicellulose	5.62	21.28	65.09

The 4-5 times higher numbers for PHC show that in testing equal concentrations for viscosity, PHC gels are much more viscous and resistant to flow than PSHusk gels. This is also consistent with the idea of greater water binding in PHC than in the husk.

6. Soluble Fiber Content Measured for PHC

The average soluble fiber content of PHC was measured for both laboratory and pilot plant produced samples. For laboratory produced PHC samples (Table 11), the soluble fiber content averaged 82%. The pilot plant PHC samples averaged 85% soluble fiber (Table 12). The minimum soluble fiber level required by the USP standard for PHC is 75%.

In comparison, in the final rule for the psyllium soluble fiber health claim, FDA assumed a PSHusk soluble fiber level of 70% to calculate a daily dose of PSHusk, based on the reviewed studies. Our analytical data for soluble fiber in PHC (~80%) reflects concentration of PHC after extraction from PSHusk and is in the same range as FDA’s assumed PSHusk soluble fiber level of 70%. This relationship supports the close compositional relationship between PHC and PSHusk before and after PSHusk extraction to remove insolubles and leave the same soluble fiber.

a. Analysis of Lab Produced PHC for Soluble Fiber

Three lots of laboratory produced PHC were tested for soluble fiber at Covance Laboratories in Madison, Wisconsin using the method of Lee and Prosky (Determination of Soluble and Insoluble Fiber in Psyllium-containing Cereal Products, Journal of AOAC International, 78,724-729, 1995). The results are presented in Table 11.

**Table 11
Comparison of Soluble and Insoluble Dietary Fiber for PHC Dietary Supplement Product-
Lab produced samples**

Lot #	Insoluble Dietary Fiber	Soluble Dietary Fiber	Total Dietary Fiber
020401-03	2.7	77.8	80.5
020701-02	3.5	79.1	82.6
020703-04	3.7	80.5	84.2
Average	3.3	79.1	82.4

b. Basis for Calculation of PHC Level in PSHusk Tested in Reported Safety Studies Based on Analysis of Multiple Pilot Plant Produced PHC Samples and Health Claim Soluble Fiber Final Rule

PHC is a polysaccharide component of psyllium husk. This polysaccharide responds to the AOAC test for Total Dietary Fiber Content as Soluble Fiber. PHC is obtained by removal of the cellulose component from PSHusk by a mild alkaline extraction. Thirteen lots of PHC, obtained

from process optimized pilot-scale batches over a two-month period, have been assayed for Soluble Dietary Fiber Content. These results are displayed below.

Table 12
Analysis of PHC Samples for soluble fiber using AOAC method

Batch Number	Soluble Dietary Fiber
1147	92.8
1148	77.4
1149	95.2
1150	81.4
1151	79.6
1152	87.5
1153	85.1
1154	84.2
1155	80.5
1156	84.5
1157	84.2
1158	80.7
1159	85.4
AVG	84.5

The average result of 84.5% soluble fiber in these batches of pilot plant produced PHC dietary supplement product reflects the removal of the cellulose component from PSHusk (85% soluble fiber for PHC vs. 70% for PSHusk). This reflects a concentration of soluble fiber in PHC relative to PSHusk, and a reduction of the insoluble fraction.

7. Fermentation Study Results

Results show that PHC is more highly fermented than PSHusk due to removal of insoluble Fraction A.

When tested, results show that both PHC and PSHusk are only slightly fermented. However PHC has double the fermentation rate of PSHusk due to removal of insolubles. This result also supports the relationship between PHC and PSHusk.

In April, 2001 a fermentation study comparing the fermentation of Fraction B (PHC) and PSHusk (psyllium ST) was carried out by Dr. George Fahey at the University of Illinois. In this study, pectin was a positive control and solka floc was a negative control. The results indicate that relative to pectin, which is highly fermented (81.16% at 12 hours), Fraction B (PHC) (14.68%) and psyllium ST (PSHusk) (5.43%) are only slightly fermented. The fact that PHC is somewhat more fermented than PSHusk is a reflection of the higher cellulose (unfermentable) content of PSHusk.

In addition, PHC is about equivalent to PSHusk in the generation of short-chain fatty acids at 12 hours, both in the types and quantities of acids generated. This is supportive of the conclusion that the same material, the arabinoxylan polysaccharide, is partially fermented in both PHC and PSHusk. These results are presented in Table 13 below.

Table 13
Fermentation of Fractions A, B, and C (B and C are PHC) Compared to PSHusk (Psyllium ST)

Sample	% DM(105 C)	% OM(DM B)	% TDF(DM B)	IN VITRO % DM DISAPPEARANCE			ACETATE PRODUCTION		PROPIONATE PRODUCTION		BUTYRATE PRODUCTION	
				0 hrs	6 hrs	12 hrs	mg/g DM		mg/g DM		mg/g DM	
				6 hrs	12 hrs	6 hrs	12 hrs	6 hrs	12 hrs	6 hrs	12 hrs	
Solka Floc®	96.31	99.77	101.23	2.92	2.00	2.83	0.13	-0.06	0.30	0.63	-0.02	-0.19
Pectin	92.78	97.74	59.75	33.06	60.72	81.16	93.25	139.46	50.42	77.37	7.02	7.58
Fraction A Extraction	94.32	89.23	88.54	9.13	10.46	12.57	7.61	9.81	3.72	4.90	0.88	0.70
Fraction B Extraction	94.57	96.97	90.88	7.02	5.72	14.68	-2.90	9.43	1.10	4.87	0.77	0.64
Fraction C Extraction	91.94	89.05	86.61	3.79	23.67	64.42	50.88	113.98	26.72	92.66	0.89	3.81
Psyllium ST	94.72	97.13	95.12	0.00	0.65	5.43	6.98	10.43	4.24	7.84	0.46	0.32

DM = Dry Matter; OM = Organic Matter; DMB = Dry Matter Basis, TDF = Total Dietary Fiber

Additionally, this study confirms that, as discussed earlier, Fraction C is more rapidly fermented than Fraction B. Fraction B is comparable to Fraction A, both poorly fermentable. PHC (Fractions B and C) is slightly more fermentable than PSHusk because of lower levels of Fraction A in PHC (15%) vs. PSHusk (20%).

8. Protein Content

Protein Content of PHC is Less Than Protein Content of PSHusk.

Protein content in PSHusk arises from contamination with psyllium seed parts. Since the psyllium seed parts are mostly insoluble, and the PHC extraction process removes insolubles, this result in a significant reduction of protein level in PHC compared with PSHusk as shown by Table 14.

Table 14
Comparison of USP Standard for Protein Content of PHC and PSHusk

Protein Content	(%w/w)
Psyllium Seed Husk	1.9
Psyllium Hemicellulose	0.5

In addition to this data, an *in-vitro* allergenicity study was done on PHC and PSHusk to confirm reduction of allergenicity. A summary of results follows which supports the fact that PHC contains a lower level of protein compared with PSHusk, resulting in lower allergenic potential.

a. Analysis of Psyllium Fractions for Protein Content

In a study by Arlian et al., several psyllium fractions were analyzed for allergen content by: 1) measuring total protein content; 2) sodium dodecylsulfate polyacrylamide gel electrophoresis (SDS-PAGE); 3) immunoblot analysis using rabbit antiserum; and, 4) immunoblot analysis of SDS-PAGE resolved proteins using human serum to identify IgE-binding allergens.

The first method showed that aqueous extraction released substantially less total protein from Fractions B (96% less) and B/C (89% less) than from the Standard raw material Psyllium (PSHusk) samples (Table 15).

Table 15
Comparison of PHC and PSHusk Total Protein Concentration Results: (Commercial Metamucil Product contains 40-60% PSHusk).

Sample	Protein Conc. ($\mu\text{g/ml}$)
Standard psyllium (PSHusk) - (H_2O extract provided by Wright State)	56
Fraction B (a separated fraction of psyllium, determined to be psyllium hemicellulose)	2
Fraction B/C (fraction C was also determined to be psyllium hemicellulose and therefore was combined with fraction B)	6

Using SDS-PAGE and immunoblot analysis, there was less protein shown in Fractions B and B/C (PHC) than in the standard PSHusk sample. Metamucil showed more protein than the test Fractions, which is to be expected since it is made up of PSHusk. Immunoblots probed with rabbit antiserum indicated that less antigenic protein was present in the Fractions.

Immunoblot analysis of SDS-PAGE resolved proteins using human serum to identify IgE-binding allergens resulted in the Standard Psyllium sample containing the largest number and highest amount of allergenic protein. Fraction B and B/C lanes showed no IgE binding at 1 day exposure and binding that was clearly less than all other samples at 4 and 7 days exposure, indicating that the allergenicity of these samples was significantly less than that of the Standard Psyllium (PSHusk). Metamucil samples showed IgE binding that was less than for Standard Psyllium but greater than for the Fractions. Fraction B contained $\leq 3.5\%$ of the allergenic protein extractable from an identical sample of Standard Psyllium, while Fraction B/C contained $\leq 4.9\%$ of the extractable allergen.

In conclusion, Fraction B contains $\sim 96\%$ less allergenic protein than Standard Psyllium (PSHusk). Fraction B/C (PHC) contains $\sim 95\%$ less allergenic protein than Standard Psyllium

(PSHusk). The dietary ingredient PHC will be clearly labeled as “psyllium hemicellulose” on the ingredient label so that individuals sensitive to inhalation or ingestion of psyllium powder can avoid exposure.

These findings clearly indicate that removal of Fraction A, high in protein, from PSHusk, results in the soluble fiber Fractions B and C (PHC), having significantly reduced protein levels.

9. Summary

As shown in this section, PHC produced by extraction of PSHusk is the major soluble fiber component of PSHusk. The analytical data presented above demonstrates that the soluble fiber in the two ingredients, PSHusk and PHC, is compositionally identical, thus leading to the conclusion that PHC is unchanged by undergoing the extraction process.

Section III

A. Description of Dietary Supplement

1. Product Form

The PHC dietary supplement raw material is a fine, odorless powder, to be marketed in either a powdered formulation (to be mixed with water) or capsule form. The fiber powder will be used by consumers to increase fiber intake beyond their normal intake from their diet, similar to currently marketed psyllium fiber supplements, by taking with water (capsule) or drinking after mixing with water (tubs or sachet). The powder will not be marketed as a conventional food ingredient or as a sole item of a meal or the diet, and will be labeled as a fiber dietary supplement. PHC will be marketed for use in products meeting the definition of “dietary ingredient” in section 201 (ff) of the Federal Food, Drug and Cosmetic Act. PHC will be clearly labeled and promoted as a dietary supplement.

2. Product Composition

There is a USP monograph for PHC that sets minimal compositional standards (e.g. Table 6, pg. 13). This dietary substance will conform to that USP monograph. Quality is controlled lot-to-lot by testing according to the USP (Pharmacopeial Forum, Vol.30 (1), Jan.-Feb.2004) specifications described earlier. Following extraction, pasteurization, neutralization, dehydration and drying, the PHC is chemically unchanged from its natural state in *Plantago ovata*, as has been shown earlier.

B. Level of Dietary Ingredient in the Dietary Supplement

1. Dietary Supplement Conditions of Use/Labeling

The powdered form of PHC will be supplied as a dietary supplement in the recommended dosage amount of 2.5 grams/dose of PHC up to three times a day. This will result in an intake of PHC of 7.5 g/day. The product will be labeled that it is not intended or recommended for use by children under 6 without a physician's guidance. The directions for use for the powdered product will be as follows:

“Directions: One heaping TEASPOON in 8 ounces of water up to three times daily. Under 6 yrs: Consult a doctor. **NOTICE:** Mix this product with at least 8 oz (a full glass) of water. Taking without sufficient liquid may cause choking. Do not take if you have difficulty swallowing.”

This is identical to the labeling used today for PSHusk, which contains 80% PHC. The ingredient statement will show “psyllium hemicellulose” so allergic individuals can avoid the product.

According to current labeled psyllium fiber products, one adult dose of powdered Metamucil® contains 3.4 g psyllium seed husk. This adult dose of Metamucil® has 2.4 grams of soluble fiber as stated on label. The proposed psyllium hemicellulose fiber products will be labeled as containing 2.5 grams of PHC per serving. This serving size will contain at least 2 grams of soluble fiber based on the fact that the soluble fiber concentration of PHC is typically 80%.

2. Mechanism of Action

PHC is Physiologically Similar to PSHusk Because PSHusk Contains 80% PHC.

PHC has the same mechanism of action as PSHusk based on comparing results of analytical, preclinical (laxation), and consumer product benefit study results under the anticipated conditions of use. PHC is considered to confer its beneficial health effects upon laxation, stool-softening, cholesterol-lowering and post-prandial glycemc response through its water-holding, polymer swelling, and gel-forming capability. It is proposed that the PHC polysaccharide in PHC and PSHusk binds water, thus increasing the stool mass, volume and lubricity, inducing peristalsis and thereby facilitating passage of the stool.

Section IV

A. Safety Assessment of Proposed Use of Psyllium Hemicellulose as a Dietary Supplement

PSHusk has a long history of safe marketing as a bulk laxative and fiber supplement at levels from 10-30 grams/day. PSHusk's primary active component is PHC, a soluble fiber component with the mechanism of action as described above.

Based on the long history of safe use of PHC as a major soluble fiber component of PSHusk, review of the safety data for PSHusk by FDA as part of the soluble fiber health claim review, and comparison of the anticipated exposure to PHC in dietary supplements to the exposure and results of the safety studies, there is a reasonable basis to conclude that PHC is safe for use as a dietary ingredient. This conclusion is based on years of safely marketing psyllium fiber (PSHusk) as a dietary supplement at comparable levels, the data presented in this notification, and the conclusion that it does not present an unreasonable risk of illness or injury under the proposed conditions of use and labeling (modeled after current psyllium dietary supplement requirements). In addition, successful consumer testing of PHC with hundreds of consumers in multiple tests did not result in any serious adverse events (Section V, Table 22, page 65).

No toxicity or adverse effects apart from rare cases of allergenicity have been reported in the literature on psyllium, psyllium husk, or psyllium hemicellulose in Medline, PubMed, Toxnet and Biosis searches by key words: adverse effects, toxicity, reproductive effects, metabolism, pharmacology, safety and either psyllium, psyllium husk or psyllium hemicellulose.

A key assumption in evaluating the safety studies for PHC is that removal of the insoluble fraction (containing cellulose, lignans, and protein) has a neutral impact on the safety of PHC. This is a reasonable assumption based on the fact that the insoluble components (removed from PSHusk to form PHC) have a very low order of toxicity, are poorly fermented in the gut, and thus are excreted intact.

While protein levels are lower in PHC versus PSHusk, this conservative assumption of neutral toxicity for the insoluble fraction assumes that the allergenicity of PHC is equivalent to that of PSHusk. Therefore, using current PSHusk labeling practices (for liquids, choking, and ingredients) should be sufficient to protect the consumer at the same level of PHC exposure.

PHC comprises 80% of PSHusk on a wet weight basis. PHC is the gel-forming viscous, polysaccharide fraction of PSHusk. Based on the identical composition of PHC and the soluble fiber in PSHusk, the safety of PHC for dietary supplement use is established clearly at the intended level of use by the data presented in this notice. This data includes referenced safety studies showing levels of PHC tested in each study (as part of PSHusk), assuming the insoluble cellulose, lignin, and protein fraction does not change the toxicity of the PHC tested. This conclusion of safety for the NDI substance is also based on two prior GRAS food use reviews of PSHusk and related psyllium components, and FDA approved Soluble Fiber Health Claim review of PSHusk of levels up to 10.2 g/day psyllium (7 g/day soluble fiber/PHC).

Comparison of Digestion and Excretion of Ingested PSHusk and PHC

As PSHusk is ingested and passes into the acidic environment of the stomach, hydration of PSHusk is accelerated and swelling of the polysaccharide portion of the husk begins. This

polysaccharide is not hydrolyzed by the stomach acids (known from *in vitro* studies), but may be partially degraded by enzymes.

As it passes out of the stomach and into the slightly alkaline environment of the intestine, hydrogen bonds linking the cellulosic portion of the PSHusk to the polysaccharide portion are cleaved. Bacterial flora in the intestine converts some of the cleavage products (from stomach enzymes) to short chain fatty acids. The polysaccharide portion; partially degraded PHC continues to hydrate and swell. This increases the viscosity and lubricity of the intestinal contents, easing the passage of stools. A gel-forming xylose/arabinose polysaccharide can be recovered from the stools of subjects fed PSHusk (US Patent #6,287,609). This polysaccharide corresponds to partially degraded PHC. Fermentation studies indicate that only about 5.4% of the PSHusk is fermented, which is equivalent to the Fraction C described earlier. Recall PSHusk is made up of Fractions A (insoluble, unfermentable cellulosic and protein), B (soluble, unfermentable polysaccharide) and C (soluble, fermentable polysaccharide). PHC is comprised of mainly Fractions B and C, after removal of most of the insoluble Fraction A during the extraction process.

Since PHC (Fractions BC) is the major polysaccharide soluble fiber component of PSHusk (Fractions ABC), the same digestion process would occur in the same way. The only difference would result from a lower level of cellulosic cleavage products, producing less gas from a lower level of short chain fatty acids produced.

1. History of Use

Psyllium has a long history of use throughout the world. Psyllium has been used in traditional medicine in India and is cited in ancient Indian Ayurvedic prescriptions. It has also been used in traditional medicine in the US, Europe, and China. Some of the uses of psyllium in traditional medicine are as laxative, emollient, demulcent, and diuretic.

As a component of PSHusk, PHC (which makes up approximately 80% of PSHusk) also has a long history of use in traditional and herbal medicine. The brand Metamucil[®], containing PSHusk, was introduced into the market in the United States over 70 years ago, has been on the

market for several decades in Europe and Canada, and continues to be marketed there and in the US as an over-the-counter bulk fiber laxative and fiber supplement. Psyllium seed husk has an excellent safety record which has been further documented by scientific groups including the Select Committee on Generally Recognized As Safe Substances (SCOGS) (1982), and the Expert Panel from the Life Sciences Research Office of the Federation of American Societies for Experimental Biology (LSRO) (1993).

In the US, in addition to fiber supplement use, PSHusk is marketed as a bulk-fiber laxative and as a component of some foods. In 1998, the Food and Drug Administration (FDA) authorized the use of a health claim in the labeling of foods and dietary supplements containing soluble fiber from PSHusk. The health claim wording used for Metamucil[®] states that diets low in saturated fat and cholesterol that include 7 grams of soluble fiber per day from PSHusk, as in Metamucil[®], may reduce the risk of heart disease by lowering cholesterol. One adult dose of Metamucil[®] powder has 2.4 grams of this soluble fiber, which is primarily comprised of PHC.

Clearly, there is a long-term history of exposure to PHC in the form of consumption of psyllium-based products, which contain high levels of PHC. The removal of the 20% insoluble materials is assumed to be neutral with respect to the conclusion of safety. While removal of insoluble protein by extraction of PSHusk to produce PHC should only reduce the risk of any allergic reaction, a conservative assumption is made here which assumes PHC will have the same allergic potential as PSHusk. While allergic reactions are rare for PSHusk today, even fewer would realistically be expected as a result of PHC exposure due to the lower protein level measured.

In supporting the safety of PHC, almost all of the referenced NDI safety studies use PSHusk as the test substance, which contains 80% PHC (Fraction BC) and 20% insoluble (cellulose, lignin, and protein) components (Fraction A). As stated earlier, where the information in the published or unpublished studies provided detailed exposure and compositional data, we were able to calculate the amount of PHC in the psyllium test doses, and these are provided in the following sections as pivotal studies to the determination of safe use of the proposed dietary substance. A

summary table of these 19 preclinical pivotal studies provides references, study type, PSHusk and PHC doses, and comparison to planned exposure levels at the beginning of Section IV. Details on the calculations of exposure to test doses are provided in Appendix A. Supportive studies, where the PHC composition could not be determined, were identified and placed separately in Appendix B, outside the body of this notice.

In addition to the PSHusk studies, we also report the results for several human consumer studies at the planned exposure level for PHC marketed product (maximum of 2.5 g PHC per serving, labeled at 3 times per day).

Using the conservative assumption of a worst case scenario (neutral toxicity for the insoluble cellulosic and protein materials, and all of the toxicity of PSH stems from PHC), combined with the calculated ratio of soluble fiber content in PSHusk to the soluble fiber content in PHC, it is possible to define the relationship of PHC, the proposed new dietary ingredient, to PSHusk, the test substance in the pivotal safety studies cited in this notice.

This calculated ratio is 67.6 (psyllium husk) / 84.5 (psyllium hemicellulose) = 0.80 .

Therefore, by multiplying the quantity of PSHusk in the safety studies by a constant factor of 0.80 it is possible to relate the safety of PSHusk to that of PHC. For example, the toxicity data for 1.0 gram of PSHusk is equivalent to the expected toxicity of 0.8 g of PHC based upon their respective contents of soluble fiber. This is so because 1.0 gram of PSHusk contains 0.676 g of soluble fiber ($1.0 \times 67.6\%$), while 0.8 grams of PHC contains 0.676 g of soluble fiber ($0.8 \times 84.5\%$).

Table 16 below shows the overall safety summary of how the test substance is quantitatively related to the amount of PHC contained in the PSHusk tested, and how this compares to consumer exposure to the intended dietary supplement. It is important to emphasize that individual safety section discussion and summary tables preceding each individual section also make it clear how the test substance is quantitatively related to the amount of PHC contained in the PSHusk tested. Exposure to the dietary ingredient PHC is then calculated based on planned labeling and product execution in powder or capsule form at levels of 2.5 g/serving. The tables

and discussion also compare the exposure level of PHC in the safety studies to the expected consumer exposure from the intended dietary supplement.

The column “Equivalent Dose of PHC” provides the exposure for PHC after taking into consideration the 80% PSHusk composition factor. The next column, “Normalized PHC Dose,” expresses the PHC exposure in amount of PHC (g) per body weight (kg) per day. The last column compares the normalized PHC dose to the proposed adult dose of 2.5 g three times daily in a 58 kg adult, which equals 0.13 g/kg/d (See Appendix A for sample calculation). This testing corresponds to an exposure of PHC (g) per body weight (kg) of 18 times the recommended adult dosing.

Table 16
Safety study summary of quantitative relationship of test substance (PSHusk) and NDI substance, (PHC)

Reference #	Study Type	Reference	Page #	Test Substance Including Dosage	Equivalent Dose of PHC	Normalized PHC Dose (g/kg body wt/day)	Test Exposure/ Recommended Dosage
1	7 day Acute – LD ₅₀ - rat	Fraschini, 1978	40	6 g/kg bw Metamucil	4.8 g/kg	2.4 g/kg	18.4
2	28 day rat (in diet)	Lawrence, 1992 HPCR 0346; Sequence #: 37051	42	10% psyllium	8%	4 g/kg/d	30.7
3	28 day rat (in diet)	Sutton & Wood, 1993 HPCR 0351; Sequence #: 37620	43	10% psyllium	8%	4 g/kg/d	30.7
4	28 day rat (in diet)	Lawrence, 1993 HPCR 0368; Sequence #: 37633	44	10% psyllium	8%	4 g/kg/d	30.7
5	91 day rat (in diet)	Lawrence, 1993 HPCR 0369b; Sequence #: 37622	44	2.5, 5.0, 10% psyllium	2% 4% 8%	1 g/kg/d 2 g/kg/d 4 g/kg/d	7.6 15.3 30.7
6	16 week beagle dog (in diet)	Fraschini, 1978	47	Meta 500mg/kg/d 1000mg/kg/d	200 mg/kg/d 400 mg/kg/d	0.2 g/kg/d 0.4 g/kg/d	1.5 3.0
7	28 weeks rat (in diet)	Coulston & Seed, 1956	49	10% blond psyllium	8%	4 g/kg/d	30.7
8	6 months dog (in diet)	Mercatelli et al., 1979	50	250 or 750 mg/kg/d	200 mg/kg/d 600 mg/kg/d	0.2 g/kg/d 0.6 g/kg/d	1.5 4.6
9	16 months monkey (in diet)	Buth & Menta, 1983	50	9.7% psyllium	7.8%	1.5 g/kg/d	11.5

Reference #	Study Type	Reference	Page #	Test Substance Including Dosage	Equivalent Dose of PHC	Normalized PHC Dose (g/kg body wt/day)	Test Exposure/Recommended Dosage
10	3 ½ yrs monkey (in diet)	Paulini et al, 1987	50	10% psyllium	8.0%	1.6 g/kg/d	12.3
11	Lifetime rat (in diet)	Carlson & Hoelzel, 1948	51	3.3% or 5% psyllium seed husk	2.6% 4%	1.3 g/kg/d 2 g/kg/d	10 15.3
12	13 week rat (in diet)	Bertram & Henderson, 1992 HPCR 0369a; sequence #: 37103	53	2.5, 5, 10% psyllium	2% 4% 8%	1 g/kg/d 2 g/kg/d 4 g/kg/d	7.6 15.3 30.7
13	1 h rat (intestinal motility)	Fraschini, 1978	55	150, 300, 600 mg/kg	60 mg/kg/d 120 mg/kg/d 240 mg/kg/d	0.06 g/kg/d 0.12 g/kg/d 0.24 g/kg/d	0.4 0.9 1.8
14	93 day rat – diet (intestinal balance)	Wood & Stoll, 1990 HPCR 0322; Sequence #: 35952	56	1, 2.5, 3.75, or 5% psyllium	0.8% 2% 3% 4%	0.4 g/kg/d 1 g/kg/d 1.5 g/kg/d 2 g/kg/d	6.1 7.6 11.5 15.3
15	6 d for 20 days, rat – catheters in abdomen aorta (blood pressure)	Fraschini, 1978	56	500 mg/kg/d Meta powder or Meta instant mix	200 mg/kg/d	0.2 g/kg/d	1.5
16	20 d rat & 30 d rabbit - gastric intubation	Fraschini 1978	58	500, 1000 mg/kg	400 mg/kg 800 mg/kg	0.4 g/kg 0.8 g/kg	3.0 6.0
17	Rabbit – oral intubation	Mercatelli et al., 1978	58	200 or 400 mg/kg/d psyllium seed husk gum	160 mg/kg/d 320 mg/kg/d	0.16 g/kg/d 0.32 g/kg/d	1.2 2.4
18	2-generation reproductive/teratology in rats (10 wks – diet)	Sutton, 1993 HPCR 0397; Sequence #: 37625	59	1, 2.5, 5% psyllium	0.8% 2% 4%	0.4 g/kg/d 1 g/kg/d 2 g/kg/d	3.0 7.6 15.3
19	Teratology in rabbits (29 d – diet (New Zealand White))	Wood, 1994 HPCR 0605: Sequence #: 37996	59	2.5, 5, or 10% psyllium	2% 4% 8%	0.6 g/kg/d 1.2 g/kg/d 2.4 g/kg/d	4.6 9.2 18.4

B. Summary of Basis to Support PHC Safety and Comparison of Exposure Levels in Safety Studies to Expected Consumer Exposure

The dietary ingredient, PHC, is reasonably expected to be safe under expected conditions of use (per label) for a number of reasons delineated in this section. First, the extracted PHC is identical to the gel-forming component of PSHusk that constitutes 80% of PSHusk. Second, there is a long history of safe PSHusk use at levels greater than the intended labeled use for PHC.

Third, there is an extensive safety database on PSHusk. Fourth, several studies conducted on PHC efficacy and consumer acceptance at planned usage levels confirm the safety profile predicted by the PSHusk database.

The lack of significant toxicological findings from any study on PSHusk and, by extension, its major component, PHC, is supportive of an excellent safety profile for the proposed dietary supplement use. PSHusk is practically non-toxic in acute animal studies at a dose of 6 grams/kg of body weight. This correlates to 4.8 g/kg of PHC, and compares to the expected consumer exposure of 0.13 g/kg/day which is based on a proposed adult dose of 2.5 g PHC three times a daily in a 58 kg adult.

There were no maternal, embryotoxic or teratogenic effects in a teratology study in rats or rabbits given up to 500 mg/kg PSHusk over most of the gestational period. This translates to an exposure level of 460 mg/kg PHC. In several early subchronic feeding studies in rats and in a limited number of dogs, PSHusk did not produce any adverse toxicological effects. Taking together, these studies whose results are presented in detail below clearly constitute a sufficient database to support the overall safety of PHC as a dietary ingredient at the labeled use level.

1. Toxicology Studies

The Select Committee on Generally Recognized as Safe Substances (SCOGS) of the Life Sciences Research Office of the Federation of American Societies for Experimental Biology evaluated the health aspects of PSHusk gum as part of Contract No. FDA 223-78-2100 (1982). In addition, The Procter & Gamble Company has conducted several safety assessment studies on psyllium. Although some of these studies have not been published, they were conducted under GLP conditions and are valuable in the evaluation of psyllium safety. Thus, they are provided to further support the safety of PHC which, as noted above, is 80% of the PSHusk tested, and removal of insolubles (cellulose and protein) is assumed to be neutral in toxicity impact. Their inclusion in this submission provides further demonstrable support for the safety of PHC.

Acute, subchronic, chronic, specialty, reproductive, teratogenicity, mutagenicity, and carcinogenicity studies on psyllium are summarized below. Since PHC comprise 80% of PSHusk, the level of PHC for each psyllium dose has been calculated and compared to the calculated consumer exposure based on dietary supplement labeling for each study grouping. Results from these preclinical studies support the overall safety of the proposed PHC dietary ingredient material at the intended level of use of 7.5 g/day.

a. Acute Toxicity Relevant to Psyllium Hemicellulose

There are no indications of adverse acute toxicity effects for PHC based on the acute toxicity testing in mice and rats. The PSHusk tested in these studies was comprised primarily (80%) of PHC, and the insolubles removed by extraction of PSHusk are assumed to be neutral with respect to PSHusk toxicity.

The LD₅₀ in mice and rats administered psyllium by gavage in an aqueous suspension of a purified Metamucil® form was greater than 6 g/kg of body weight (Fraschini, 1978). No deaths occurred within a 7-day observation period. This PSHusk test dose corresponds to 4.8 g/kg PHC.

Table 17 below summarizes this testing. The PHC level for the PSHusk dose was calculated and compared to the calculated consumer exposure based on intended dietary supplement labeling. The column “Equivalent Dose of PHC” provides the exposure for PHC after taking into consideration the 80% PSHusk composition factor. The next column, “Normalized PHC Dose,” expresses the PHC exposure in amount of PHC (g) per body weight (kg) per day. When investigators described PSHusk exposure as a percentage of feed, and failed to report feed consumption, conservative estimates of daily feed consumption for the rat (5% of body weight) were used to calculate the entry for the “Normalized PHC Dose” column. The last column compares the normalized PHC dose to the proposed adult dose of 2.5 g three times daily in a 58 kg adult, which equals 0.13 g/kg/d. This testing corresponds to an exposure of PHC (g) per body weight (kg) of 18 times the recommended adult dosing.

**Table 17
Acute Toxicity Conducted on PSHusk Which Contains 80% PHC**

Reference number	Study Type	Reference	Test Substance Including Dosage	Equivalent Dose of PHC*	Normalized PHC Dose (g/kg body wt/day)	Test Exposure/ Recommended Dosing**
1	7 d Acute – LD ₅₀ - rat	Fraschini, 1978	6 g/kg bw Metamucil	4.8 g/kg	2.4 g/kg	18.4

* PHC is 80% of PSHusk tested

**Dietary supplement labeled dose is 0.13 g/kg/day

b. Subchronic Studies Relevant to Psyllium Hemicellulose

There were no significant adverse subchronic toxicity effects observed for PHC based on five subchronic PSHusk studies in several different species tested for days to weeks. The PSHusk tested in these studies is relevant to PHC safety since PSHusk is comprised of 80% PHC, and the insolubles removed from PSHusk during extraction are assumed to be neutral, as previously discussed.

The five preclinical studies summarized in the table below evaluated the subchronic safety of PSHusk and PHC oral exposure in the rat and dog. In all five studies, there were no adverse effects observed for either PSHusk or PHC, providing a reasonable basis for an identical conclusion relative to the safety of the PHC dietary ingredient material that is the subject of the Notification under expected conditions of use.

In Table 18, the PHC level for each PSHusk dose has been calculated and compared to calculated consumer exposure based on intended dietary supplement labeling. The column “Equivalent Dose of PHC” provides the exposure for PHC after taking into consideration the 80% PSHusk composition factor. The next column, “Normalized PHC Dose,” expresses the PHC exposure in amount of PHC (g) per body weight (kg) per day. When investigators described PSHusk exposure as a percentage of feed and failed to report feed consumption, a conservative estimate of daily feed consumption for the rat (5% of body weight) was used to calculate the entry for the “Normalized PHC Dose” column (Appendix A). The last column

compares the normalized PHC dose to the proposed adult dose of 2.5 g three times daily in a 58 kg adult, which equals 0.13 g/kg/d (See appendix A for sample calculation). These preclinical studies correspond to daily exposures of PHC (g) per body weight (kg) ranging from 1.5 to over 30 times that of the recommended adult dosing.

Table 18
Summary of Subchronic Studies Conducted on PSHusk Which Contains 80% PHC

Reference Number	Study Type	Reference	Test Substance Including Dosage	Equivalent Dose of PHC*	Normalized PHC Dose (g/kg body wt/day)	Test Exposure/ Recommended Dosing**
2	28 day rat (in diet)	Lawrence, 1992 HPCR 0346	10% psyllium	8%	4 g/kg/d	30.7
3	28 day rat (in diet)	Sutton & Wood, 1993 HPCR 0351	10% psyllium	8%	4 g/kg/d	30.7
4	28 day rat (in diet)	Lawrence, 1993 HPCR 0368	10% psyllium	8%	4 g/kg/d	30.7
5	91 day rat (in diet)	Lawrence, 1993 HPCR 0369b	2.5, 5.0, 10% psyllium	2% 4% 8%	1 g/kg/d 2 g/kg/d 4 g/kg/d	7.6 15.3 30.7
6	16 week beagle dog (in diet)	Fraschini, 1978	Meta 500mg/kg/d 1000mg/kg/d	200 mg/kg/d 400 mg/kg/d	0.2 g/kg/d 0.4 g/kg/d	1.5 3.0

* PHC is 80% of PSHusk tested

**Dietary supplement labeled dose is 0.13 g/kg/day

i. Discussion of Key Subchronic Toxicity Data on PSHusk and Relevance to PHC

A 28-day feeding study was conducted by P&G at Hazelton Laboratories (HPCR 0346; Lawrence, 1992) whereby 10% psyllium was administered in feed. The 10% PSHusk dose is equivalent to a dose of 8% PHC.

Male and female Crl:CO BR/VAF/Plus™ (10 animals/sex/treatment) were randomly assigned to treatments of diets containing 0 or 10%, psyllium, the only in-life observation was that of long, slender, stringy feces in psyllium-fed rats. The only changes noted were decreases in weight

gain in both sexes receiving psyllium. Trends in food consumption were difficult to assess due to excessive spillage. Lower serum total protein, albumin, globulin, and total iron binding capacity were observed in both sexes receiving psyllium and resulted in lower urine volume and higher urine specific gravity in males and a higher urine pH in males and females. Although these changes were considered biologically relevant they were not of concern from a toxicological perspective. Males fed psyllium also had higher absolute and relative weights of colon/rectum/anus. There were no treatment related macroscopic or microscopic findings were observed.

A follow-up 28-day feeding study (HPCR 0351; Sutton and Wood, 1993) with 10 % psyllium (8% PHC) in the diet was conducted using male and female Fischer-344 rats (10/sex/group) by P&G at Hazelton Laboratories. Animals received either 0 or 10% psyllium (0 or 8%PHC), 10% cellulose or 10% guar gum in the diet. Long stringy feces were noted in animals receiving the psyllium, but no other test substance-related effects were reported during the in-life observation period or from the ophthalmic examinations. Mildly lower serum total protein, albumin, globulin, and total iron binding capacity were observed in both sexes and appeared to be psyllium related; however none of these effects are considered of toxicological concern. Lower levels of calcium were statistically significant in males only. Both males and females were reported to have higher Alanine aminotransferase (ALT) and higher urine pH. Again, although these were considered biologically relevant, they were not of concern from a toxicological perspective. That is, these were very small changes that were not supported by any other clinical or pathologic findings. Slightly lower terminal body weights were reported for males receiving psyllium as compared to controls and cellulose, slightly higher terminal body weights were reported when compared to rats fed guar gum. Females tended to weigh more than rats on the other three diets.

In general, animals on the psyllium diet consumed more food than animals on the other treatments (except psyllium fed males as compared to males on cellulose diet). There were no treatment-related macroscopic or microscopic findings. Differences in absolute and relative organ weights were found for adrenals, both kidneys, and liver of males and for

cecum/rectum/anus and large intestine of both males and females. These changes in intestinal weight were further investigated in additional studies. The reader is referred to the section below on morphometric analysis (page 53). P&G conducted another 28-day feeding study (HPCR 0368; Lawrence, 1993) with lower dosing of psyllium (5% psyllium (equivalent to 4% PHC) in diet) at Hazelton Laboratories, North America to evaluate the short-term toxicity of psyllium. Male and female weanling Sprague-Dawley rats (10 animals/sex/treatment) were randomly assigned to treatments of diets containing 0, 1.0 %, 2.5 %, or 5.0 % psyllium (equivalent to 0, 0.8, 2.0, or 4% PHC). The only in-life observation was that of dark, irregularly shaped feces noted for all rats consuming psyllium diets. The only changes noted were a significant decrease in weight gain, increases in food consumption and dramatic increases in water consumption in males but not in females with increasing dosage. Higher absolute and relative organ weights were noted for cecum and large intestine in the high-dose males and in all psyllium-fed females. Males fed 5 % psyllium (equivalent to 4% PHC) also had higher absolute and relative weights of colon/rectum/anus. No treatment related macroscopic or microscopic findings were observed. Mean psyllium consumption for animals fed 5% psyllium (equivalent to 4% PHC) ranged from 3.9 to 5.2 grams/kg/day for males and from 4.6 to 5.5 grams/kg/day for females. This PSHusk exposure range translates to PHC consumption levels of 3.3 to 4.1 g/kg/day and 3.7 to 4.4 g/kg/day respectively.

Procter & Gamble conducted a 91-day subchronic toxicity study (HPCR 0369b; Lawrence, 1993) at Hazelton Laboratories, North America in male and female Fischer 344 rats. Male and female rats were assigned to six groups of 20 animals/sex. PSHusk was fed at levels of 0, 2.5, 5.0, or 10.0 % (w/w) of the diet, equivalent to PHC levels of 0, 2, 4, or 8% w/w. In addition, cellulose and guar gum were fed at 10 % (w/w) of the diet. The changes of interest worth noting were between the cellulose and psyllium/PHC groups; other inter-group comparisons are not discussed. No deaths occurred during the study period. Dry, dark, irregularly shaped feces and soft mucoid-like stool were noted for all psyllium-fed rats. No test-substance related effects were noted during ophthalmic examinations. Males fed 10 % psyllium (8% PHC) tended to weigh less and have lower cumulative body weight gains than the 10 % cellulose fed animals until week four. This was not observed in females. Weekly food consumption and food efficiencies varied between groups and were not judged to be toxicologically meaningful. Psyllium-fed

animals consumed more water than the cellulose group and the increases in water consumption in the psyllium-fed groups were dose-related. Lower terminal body weights were seen in animals given 10 % psyllium (8% PHC). Higher absolute and relative organ weights were noted for cecum, colon/rectum/anus, and large intestine. The organ weight increases were dose-related. These weight increases were investigated further and are discussed in the section on morphometric analysis below. No test-related macroscopic or microscopic findings were seen. Mean psyllium consumption data was as follows: for males the 2.5 and 5.0 % psyllium (2 and 4% PHC) diets provided 1.8 and 3.6 grams/kg body weight/day psyllium (1.4 and 2.9 g/kg/day PHC). The 10 % psyllium (8% PHC) diet provided 7.3 grams/kg body weight/day (5.9 g/kg/day PHC). For females, the 2.5 and 5.0 % psyllium (2 and 4% PHC) diets provided 2.1 and 4.3 grams/kg body weight/day (1.9 and 3.5 g/kg/day PHC) while the 10% psyllium (8% PHC) diet provided 8.7 grams/kg body weight/day (7 g/kg/day PHC).

Psyllium-related changes in clinical pathology in both males and females included lower total serum protein, albumin, and globulin in the psyllium-fed groups as compared to the 10% cellulose groups (with the exception of the low dose psyllium (PHC) males). Compared to the 10% cellulose group, serum cholesterol was lower in the low dose males and high dose females at 28 days and in high dose males and all females at 91 days. Higher serum ALT levels and lower serum alkaline phosphatase (91d only), calcium, phosphorus (28d only) and total iron binding capacity (TIBC) were reported in high dose psyllium males as compared to the 10% cellulose males. Males fed 5% psyllium (4% PHC) had higher ALT, lower alkaline phosphatase (91 days only) and lower calcium and potassium. Males fed 2.5% psyllium (2% PHC) had lower serum potassium and higher TIBC. Females fed 10% psyllium (8% PHC) had higher aspartate aminotransferase (AST), ALT and alkaline phosphatase (91 days only) and lower calcium, potassium, and TIBC compared to those fed 10% cellulose. Females fed 5% psyllium (4% PHC) had higher ALT, AST (91 days only) and alkaline phosphatase values than those fed 10% cellulose. Serum ALT was higher in females fed 2.5% psyllium (2% PHC) compared to those fed 10% cellulose. **It was concluded that these changes were of toxicologically significance and were considered to be adaptive responses to high levels of psyllium (PHC) in the diet.** The basis for this conclusion follows.

Although elevations in serum ALT and AST are often used as an indicator of liver damage, the lack of differences in liver weight as a percentage of body weight, and the absence of any histopathological changes in the livers of rats fed psyllium provide strong support against such a correlation in this study. The aminotransferases are enzymes involved in the elimination of nitrogen from amino acids to provide alpha-keto acids for the tricarboxylic acid cycle and gluconeogenesis. They play important roles in normal energy homeostasis in the utilization of both exogenous (dietary) and endogenous (metabolic turnover of body protein) amino acids; serum ALT levels have been shown to correlate with the induction of gluconeogenesis. It is well known that soluble fibers like PSHusk and PHC decrease postprandial blood glucose levels, which could, in turn, potentially create a stimulus for increased gluconeogenesis, thus resulting in elevated ALT concentrations.

The lower serum total protein, albumin and globulin concentrations are consistent with the hypothesis that some protein was being utilized for gluconeogenesis. The fact that the concentrations of these proteins in rats fed psyllium for 91 days were no lower than values observed at 28 days indicates that this was not a progressive effect. The findings that there were no increases in urinary protein, no evidence of gastrointestinal pathology which could account for protein loss, and no differences in growth or feed efficiency in rats fed psyllium (with 80% PHC) provide strong evidence for the lack of an adverse effect on protein metabolism. Therefore, it is likely that these changes are only a reflection of the establishment of a new metabolic steady state.

The elevated alkaline phosphatase levels in rats fed psyllium are not considered biologically significant, since the differences were small, not entirely dose-dependent and not observed in males. The lower serum iron, calcium and TIBC values are likely due to the lower serum protein concentrations, since a considerable proportion of iron and calcium are protein bound, and TIBC is a measure of transferrin, which is a beta-globulin. Lower serum cholesterol was an expected finding, since psyllium (with 80% PHC) has been shown to be an effective hypocholesterolemic agent in both experimental animals and in humans. The lower serum creatine levels in rats fed

10% psyllium (8% PHC) are consistent with its increased urinary excretion associated with higher urine volumes, which are likely to have resulted from the increased water consumption.

Males fed all levels of psyllium had higher urine pH values than those fed 10% cellulose; males fed 10% psyllium (8% PHC) had higher urine volumes at 91 days. Females fed 5% or 10% psyllium (4 or 8% PHC) had higher mean urine volume, lower specific gravity and higher urine pH than did rats fed 10% cellulose. The increase in urine pH is consistent with the induction of gluconeogenesis by the kidney. Increased gluconeogenesis in the kidney results in glutamine being converted to glutamate, with ammonium ions being released into the urine, resulting in its alkalinization. The loss of these hydrogen ions results in a mild metabolic alkalosis. Under this condition, hydrogen ions leave intracellular sites to balance the serum pH; cellular potassium is then redistributed from the serum to the intracellular sites to balance the intracellular monovalent cation concentration. Previous work has shown that both urinary and fecal potassium are actually decreased in a dose-dependent manner in rats fed psyllium (providing 80% PHC), demonstrating that the lower serum levels do not reflect body losses.

Another subchronic oral toxicity study was also conducted by Fraschini (1978) in male and female beagle dogs dosed with aqueous mixtures of Metamucil[®] powder at 500 and 1,000 mg/kg/day and Metamucil[®] Instant Mix at 1,000 mg/kg/day six days a week for 16 weeks. These PSHusk dose levels correspond to 400, 800, and 800 mg/kg/day PHC respectively. No adverse effects due to treatments were noted in hematological, blood and urine chemistries or in histologic evaluation of a variety of organs.

Two additional supportive studies can be found in Appendix B.

c. Chronic Studies Relevant to PHC- Psyllium Hemicellulose

There are no significant adverse effects observed in the chronic toxicity data for PHC based on 5 chronic PSHusk studies in several different species tested for weeks to years. The PSHusk studies are relevant to the safety of PHC since the PSHusk tested in these studies is comprised of

80% PHC, and the insolubles removed during extraction are assumed to be neutral with respect to toxicity.

The five preclinical studies summarized in the table below evaluated chronic oral exposure of both PSHusk and PHC in the rat, dog and monkey. In total, these five PSHusk studies demonstrate the overall safety of the PHC which is the subject of this Notification, with safety factors of 2-31 for expected dietary supplement exposure and a long history of safe use of PSHusk which contains 80% PHC.

In Table 19 below, the PHC level for each PSHusk dose has been calculated and compared to calculated consumer exposure based on dietary supplement labeling. The column “Equivalent Dose of PHC” provides the exposure for PHC after taking into consideration the 80% PSHusk composition factor. The next column, “Normalized PHC Dose,” expresses the PHC exposure in amount of PHC (g) per body weight (kg) per day. When investigators described PSHusk exposure as a percentage of feed and failed to report feed consumption, conservative estimates of daily feed consumption for the rat (5% of body weight) and monkey (2% of body weight) were used to calculate the entry for the “Normalized PHC Dose” column (Appendix A). The last column compares the normalized PHC dose to the proposed adult dose of 2.5 g three times daily in a 58 kg adult, which equals 0.13 g/kg/d (see calculation sample in appendix A). These preclinical studies correspond to daily exposures of PHC (g) per body weight (kg) ranging from 1.5 to over 30 times that of the recommended adult dosing of 7 g/day PHC.

Table 19
Summary of Chronic Studies Conducted on PSHusk Which Contains 80% PHC

Reference Number	Study Type	Reference	Test Substance Including Dosage	Equivalent Dose of PHC*	Normalized PHC Dose (g/kg body wt/day)	Test Exposure/Recommended Dosing**
7	28 week rat (in diet)	Coulston & Seed, 1956	10% ground blond psyllium seed	8%	4 g/kg/d	30.7

Reference Number	Study Type	Reference	Test Substance Including Dosage	Equivalent Dose of PHC*	Normalized PHC Dose (g/kg body wt/day)	Test Exposure/ Recommended Dosing**
8	6 month dog (in diet)	Mercatelli et al., 1979	250 or 750 mg/kg/d purified psyllium husk gum	200 mg/kg/d 600 mg/kg/d	0.2 g/kg/d 0.6 g/kg/d	1.5 4.6
9	16 month monkey (in diet)	Buth & Menta, 1983	9.7% psyllium	7.8%	1.5 g/kg/d	11.5
10	3½ year monkey (in diet)	Paulini et al, 1987	10% psyllium husk	8.0%	1.6 g/kg/d	12.3
11	Lifetime rat (in diet)	Carlson & Hoelzel, 1948	3.3% or 5% psyllium seed husk	2.6% 4%	1.3 g/kg/d 2 g/kg/d	10 15.3

* PHC is 80% of PSHusk tested

**Dietary supplement labeled dose is 0.13 g/kg/day

i. Discussion of Key Chronic Toxicity Data on PSHusk and Relevance to PHC

The 1982 LSRO (Life Sciences Research Organization) FASEB SCOGS report included chronic work by Coulston and Seed. In this study, Sprague-Dawley rats fed a commercial diet containing 10% ground PSHusk (8% PHC), commonly called blond psyllium (*P. ovata*), for 28 weeks exhibited no changes except mild laxation (Coulston and Seed, 1956). The authors also reported a brown pigment in the kidneys that was found only in the animals fed the seed hulls which had the mucilaginous (gel-forming viscous fraction, PHC) portion removed. No evidence of the brown pigment was evident in histological preparations and the authors concluded that the lack of reports of kidney pigmentation in humans exposed to psyllium is good evidence that humans are not affected or pigmentation is so minimal that it is not recognizable histologically. As indicated in the table above, the test dose of 10% PSHusk corresponds to 8% PHC and represents a 30-fold factor over the expected human exposure from dietary supplement use of PHC as labeled.

The SCOGS report also included a review of a longer chronic study by Mercatelli et al., (1979). This group conducted a 6-month toxicity study in male and female dogs. In this study, beagle dogs (10-12 months of age) were fed 250 or 750 mg/kg/day of purified PSHusk gum (*P. ovata*) for 6 months with no biochemical, hematological or urinary changes. These doses are equivalent to 200 or 600 mg/kg/day PHC. Dose-effect relationships appeared to exist regarding decreases in total serum protein, total cholesterol and glucose in treated males. Blood cholesterol was lower at 16 weeks. There were no histological changes observed in heart, lungs, kidneys, spleen, and adrenals, thyroid, pancreas, testes, ovaries or gastrointestinal tract. As indicated above, the test dose of PSHusk represents 2-5 times the expected human exposure from dietary supplement use of PHC as labeled.

Buth and Mehta (1983) evaluated the effect of PSHusk on iron availability in African Green monkeys fed a semi-purified diet supplemented with either 9.7% psyllium (7.8% PHC) or cellulose for 16 months. Iron absorption was measured by intubation with $^{59}\text{FeCl}_3$. Monkeys in the psyllium group absorbed more iron than did those on the cellulose diet. The cumulative daily losses of Fe^{59} showed delayed excretion in the psyllium group.

Paulini et al., (1987) fed 10 adult male African Green monkeys diets containing either 10% PSHusk (8% PHC) or 10% cellulose for three and one half years. Four monkeys consumed the psyllium diet, 6 monkeys received the cellulose diet. One month prior to termination, two of the cellulose-fed monkeys were switched to a nonpurified monkey chow with 2.5% crude fiber. No signs of adverse histopathologic effects were seen upon examination by light microscopy using Scanning Electron Microscopy (SEM). The SEM examination did reveal mild cellular swelling and disarray at villous tips throughout the small intestine in the psyllium group and in the duodenum in the cellulose group. Mucosal height and muscle layer thickness were reduced in the psyllium group. No differences in the colon were found by SEM. The authors concluded that long-term psyllium ingestion may lead to epithelial cell loss and muscle layer hypertrophy in the small intestine and thinning of the colon wall. This study was reviewed by P&G Veterinary pathologists (T.A. Bertram and G.R. Johnson). It was documented in an internal memo (4/26/89) by Bertram that there were numerous methodological, technical, and experimental design errors

which make the study's conclusions suspect. For example, no baseline diet was used, there was no indication of how clinical data were obtained or evaluated and no explanation was given for why two animals were switched from the cellulose group to monkey chow.

The histology slides from this study were obtained by P&G from Washington State University and the intent was to have outside pathology peer review. However, when G. Johnson evaluated the slides (internal memo dated 1/13/87), it was concluded that the slides were in such poor quality (not properly fixed prior to preservation) with multiple artifacts that there would be no value in any peer review. It was speculated that without careful control of fixation, measurements of tissue compartment thicknesses could be imprecise and inaccurate. Such a problem is "magnified" when a low number of animals exist in treatment groups. A review by an internal P&G Scientific Review Group concluded that the findings of these authors indicating psyllium may have caused intestinal lesions are not supported. This issue was conclusively addressed by FDA during the development of the Soluble Fiber Health Claim Final Rule published in 1998. The agency also concluded that there wasn't sufficient evidence to support concern over this issue based on the evidence reviewed. No new information has changed this conclusion in the intervening years.

The only lifetime psyllium feeding study was done pre-GLP in 1948 and is presented in the SCOGS report. Carlson and Hoelzel (1948) reported that feeding rats mixtures of 3.3% or 5% PSHusk (equivalent to 2.7 or 4% PHC) and semi-fibrous cellulose flour or ground kapok in the diet had no deleterious effect. The rats in the treated groups were reported to have longer lifespans than rats fed the basal low-residue diet. However, the sample size was small (n=2-3/sex) thus making it difficult to provide conclusive data.

d. Specialty Studies Relevant to PHC- Psyllium Hemicellulose

Four specialty studies summarized below in Table 4 which evaluated the effects of psyllium (and thus PHC) on 1) morphology of the large intestine, 2) intestinal motility, 3) mineral balance, and 4) blood pressure in rats or mice and rats. Study duration ranged from one to 93 days.

There were no gross morphological or histological alterations in the large intestine. The observed increases in rat large intestinal weights were considered to reflect increases in cecal and colonic/rectal/anal length. Intestinal motility was increased following psyllium administration, a finding anticipated for psyllium products. There were no adverse effects on mineral excretion or status, nor on arterial pressures and cardiac rates.

These data support the overall safe use of PHC since PHC makes up 80% of PSHusk. The remaining 20% which consists of protein and cellulosic material is assumed to be neutral from a toxicological standpoint. Therefore, these specialty studies on psyllium provide key safety information on PHC.

These four Specialty studies are summarized in the Table 20 below. In this table, the PHC level for each PSHusk dose has been calculated and compared to the calculated consumer exposure based on dietary supplemental labeling. The column “Equivalent Dose of PHC” provides the exposure for PHC after taking into consideration the 80% PSHusk composition factor. The next column, “Normalized PHC Dose” expresses the PHC exposure in the amount of PHC (g) per body weight (kg) per day. The last column compares the normalized PHC dose to the proposed adult dose of 2.5 g three times daily in a 58 kg adult, which equals 0.13 g/kg/d. Dose levels in the Specialty studies correspond to daily exposure of PHC (g) per body weight (kg) ranging from 0.4 to over 30 times that of the recommended adult dosing.

Table 20
Specialty Studies Conducted on PSHusk which Contain 80% PHC

Reference Number	Study Type	Reference	Page #	Test Substance Including Dosage	Equivalent Dose of PHC*	Normalized PHC Dose (g/kg body wt/day)	Test Exposure/ Recommended Dosing**
12	13-week rat	Bertram & Henderson, 1992 HPCR 0369a	28	2.5, 5, 10% psyllium	2% 4% 8%	1 g/kg/d 2 g/kg/d 4 g/kg/d	7.6 15.3 30.7
13	1 h rat – (intestinal motility)	Fraschini, 1978	29	150, 300, 600 mg/kg	60 mg/kg/d 120 mg/kg/d 240 mg/kg/d	0.06 g/kg/d 0.12 g/kg/d 0.24 g/kg/d	0.4 0.9 1.8

Reference Number	Study Type	Reference	Page #	Test Substance Including Dosage	Equivalent Dose of PHC*	Normalized PHC Dose (g/kg body wt/day)	Test Exposure/ Recommended Dosing**
14	93 d rat – diet (mineral balance)	Wood & Stoll, 1990 HPCR 0322	30	1, 2.5, 3.75, or 5% psyllium	0.8% 2% 3% 4%	0.4 g/kg/d 1 g/kg/d 1.5 g/kg/d 2 g/kg/d	6.1 7.6 11.5 15.3
15	6 d/wk for 20 days; rat – catheters in abdominal aorta (blood pressure)	Fraschini, 1978	30	500 mg/kg/d Meta powder or Meta instant mix	200 mg/kg/d	0.2 g/kg/d	1.5

* PHC is 80% of PSHusk tested

**Dietary supplement labeled dose is 0.13 g/kg/day

i. Discussion of Key Specialty Studies on PSHusk and Relevance to PHC

- **Morphometric Analysis of the Lower Gastrointestinal Tract of Rats from the 91-Day Study**

In order to address the clinical pathology changes observed in the 91-day study (HPCR-0369b; Lawrence, 1993), P&G conducted an extensive microscopic evaluation to identify the tissue compartments responsible for a large intestinal (cecum/rectum/anus) weight increase observed in the study referenced above, where male and female rats were fed 2.5, 5 or 10 % w/w psyllium (2, 4, or 8% PHC), or cellulose or guar gum at 10% w/w of the diet for 13-weeks (HPCR 0369a; Bertram & Henderson, 1992). Three (3) slides with four (4) mounted sections from the large intestine (cecum, proximal colon, middle colon, and distal colon/rectum/anus) were evaluated for each of the one hundred and sixty (160) Fischer 344 rats (80 male and 80 female) from the 91-day subchronic study conducted at Hazelton Laboratories, North America for P&G. Evaluation was done using an automated computer-assisted image analysis system to quantify mucosal and non-mucosal tissue compartment areas of the large intestine. Rats were randomly assigned to four groups (20/sex/group) that had been given the basal diet (control), 10 % PSHusk (8% PHC), 10 % Avicel (cellulose), or 10 % guar gum.

The primary measurement generated was the absolute areas of the mucosal and nonmucosal tissue compartments in the cecum and colon/rectum/anus. Secondary endpoints, that were calculated from the primary endpoints, included the relative area (percentage) of each tissue compartment to the total area measured (mucosa and nonmucosa) and the respective absolute weight of each compartment. Additionally, the endpoints were summed for each segment (cecum/rectum/anus) to determine endpoint values for the entire large intestine.

In both male and female rats, the increase in large intestine, cecum, and colon/rectum/anus weights observed with psyllium (PHC) was associated with increases in the weight of both mucosal and nonmucosal compartments. For the large intestine, these weight changes involved changes in nonmucosal cross-sectional area for males and females as compared with basal diet fed animals (16% and 34% respectively). Mucosal cross-sectional area was only increased in females (about 25%) and not at all in males.

For the cecum, the weight changes in male rats were not associated with any change in cross-sectional area and can be considered a result of uniform increase in cecal length. In females, there were increases in cross-sectional area of mucosal and nonmucosal compartments of about 31% and 66% respectively, which are sufficient to account for the majority of the increased caecal weight.

For the colon/rectum/anus, the weight changes for both males and females involved increases in cross-sectional area of both mucosal (about 18% and 17% respectively) and nonmucosal (about 22% and 21% respectively) compartments. In females, these changes were sufficient to probably account for the increase in weight of the colon/rectum/anus. However, this was not true for males, again suggesting an increase in length.

From this study, it is concluded that increases in large intestinal weight of male rats induced by feeding PSHusk (containing 80% PHC) reflect a minimal increase in the nonmucosal and mucosal cross-sectional area and that most of the weight increase is the result of increased

intestinal length. In contrast to male rats, female rats had substantial increases in the cross-sectional area of the cecum and colon primarily associated with the nonmucosal compartment. This accounted for much of the increased large intestinal weight. The pathologists noted that when compared to control diets containing the same level of fiber (Avicel and guar gum), increases in large intestinal weight induced by psyllium (80% PHC) were considered to reflect increases in cecal and colonic/rectal/anal length and not increases in circumference as a result of selective mucosal or nonmucosal compartment hypertrophy. These expert pathologists concluded that increases of intestinal weight that are the result of increased length are considered to be the result of adaptive alterations in the intestine and are not considered to be of toxicological risk. This assessment is supported by the lack of any gross morphological or histological alterations in the large intestine (cecum and colon/rectum/anus) of these psyllium-treated animals.

Fraschini (1978) also used male Swiss mice and Sprague-Dawley rats to study the effects of Metamucil® on the intestinal canal and peristalsis. All animals were given a suspension of 10% charcoal in 5% gum Arabic, with Metamucil® added to it for the test animals at doses of 150, 300 and 600 mg/kg body weight, by gastric lavage. The equivalent PHC doses from the Metamucil are 120, 240, and 480 mg/kg/day. Animals were sacrificed after one hour and the progress of the charcoal in the intestine was assessed on the basis of its location in the intestine. Results showed for both species that PSHusk in Metamucil® (containing 80% PHC) has the ability to stimulate intestinal motility. Fraschini (1978) also showed that even under conditions of decreased peristalsis, Metamucil® (and thus PHC) has the ability to stimulate intestinal motility. Using nicotine to depress peristaltic activity, similar doses of 150, 300 and 600 mg/kg body weight Metamucil® helped to normalize the rate of intestinal transit. These doses are equivalent to 120, 240, and 480 mg/kg/day PHC.

- **Effect of Dietary Psyllium on Mineral Balance**

P&G conducted a 93-day study in 8 week old male Fischer 344 rats to assess the effect of psyllium (and thus PHC) on mineral balance (HPCR0322; Wood and Stoll, 1990). Animals were either fed a fiber-free diet or a diet with psyllium at levels of 0, 1.0, 2.5, 3.75 or 5% (w/w) with

cellulose added to yield a total dietary fiber level of 5.0%. These doses correspond to 0, 0.8, 2, 3, or 4% PHC. Diets contained either 0.25% calcium or 0.5% calcium. The effect of these dietary fibers on the absorption of minerals (Ca, P, Mg, Fe, Cu, Mn, Zn, Na and K) was investigated. Fecal and urinary mineral excretion were measured at Days 30 and 86 and normalized for intake. Serum and bone mineral concentrations were determined after 93 days. When viewed collectively, the data indicate that the supplementation of diets with cellulose or psyllium (PHC) had no adverse effects on the mineral excretion or status.

- **Effects of Psyllium on Blood Pressure**

The cardiocirculatory effects of PSHusk and thus PHC were evaluated by Fraschini (1978). Male Sprague-Dawley rats with in-dwelling blood pressure catheters in the abdominal aorta via the femoral artery were administered Metamucil® powder (500 mg/kg/day) or Metamucil® Instant Mix (500 mg/kg/day) for six days /week for a period of 20 days. Arterial pressures and cardiac rates were unchanged due to treatments. These treatment levels correspond to 400 mg/kg/day PHC in both cases.

- e. **Reproduction and Teratogenicity**

Five reproductive/teratogenicity studies are summarized including a rat reproductive study, two rabbit reproductive studies, a rat two-generation reproductive and teratology study, and a rabbit teratology study.

In the rat and rabbit reproductive studies, there were no deleterious effects reported. In the two-generation rat reproductive and teratology study, the no-observable-adverse effect levels for psyllium were 5% (4% PHC) for mating performance and fertility, 1% (0.8% PHC) for offspring growth and development, and 5% (4% PHC) for fetal development and teratogenesis. For the rabbit teratology study, the no-observable-adverse effect level for developmental toxicity was 10.0% (8% PHC) based on the lack of adverse fetal findings. Ingestion of psyllium at the 10% (8% PHC) level resulted in lower maternal body weights, lower body weight gains, and lower

water consumption. The 5% and 10% psyllium dose levels (4 and 8% PHC) are 9-18 times that of the recommended adult dose.

These data support the overall safe use of PHC since PHC makes up 80% of PSHusk composition with the remaining 20% insoluble protein and cellulosic material assumed to be toxicologically neutral. Therefore, these specialty studies provide relevant safety information on PHC.

The five reproductive/teratogenicity studies are summarized in Table 21 below. In this table, the PHC level for each PSHusk dose has been calculated and compared to the calculated consumer exposure based on dietary supplemental labeling. The column “Equivalent Dose of PHC” provides the exposure for PHC after taking into consideration the 80% PSHusk composition factor. The next column, “Normalized PHC Dose” expresses the PHC exposure in the amount of PHC (g) per body weight (kg) per day. The last column compares the normalized PHC dose to the proposed adult dose of 2.5 g three times daily in a 58 kg adult, which equals 0.13 g/kg/d. Dose levels in the reproductive/teratogenesis studies correspond to daily exposure of PHC (g) per body weight (kg) ranging from 1.2 to over 18 times that of the recommended adult dosing.

**Table 21
Reproduction and Teratogenicity Studies Conducted on PSHusk which Contain 80% PHC**

Reference number	Study Type	Reference	Page #	Test Substance Including Dosage	Equivalent Dose of PHC*	Normalized PHC Dose (g/kg body wt/day)	Test Exposure/Recommended Dosing**
16	20 d rat & 30 d rabbit - gastric intubation	Fraschini, 1978	30	500, 1000 mg/kg	400 mg/kg 800 mg/kg	0.4 g/kg 0.8 g/kg	3.0 6.0
17	Rabbit – oral intubation	Mercatelli et al., 1978	30	200 or 400 mg/kg/d psyllium seed husk gum	160 mg/kg/d 320 mg/kg/d	0.16 g/kg/d 0.32 g/kg/d	1.2 2.4

Reference number	Study Type	Reference	Page #	Test Substance Including Dosage	Equivalent Dose of PHC*	Normalized PHC Dose (g/kg body wt/day)	Test Exposure/Recommended Dosing**
18	2-generation reproductive/teratology study in rats (10 wks - diet)	Sutton, 1993 HPCR 0397	31	1, 2.5, 5% psyllium	0.8% 2% 4%	0.4 g/kg/d 1 g/kg/d 2 g/kg/d	3.0 7.6 15.3
19	Teratology study in rabbits (29 d – diet (New Zealand White))	Wood, 1994 HPCR 0605	33	2.5, 5, or 10% psyllium	2% 4% 8%	0.6 g/kg/d 1.2 g/kg/d 2.4 g/kg/d	4.6 9.2 18.4

* PHC is 80% of PSHusk tested

**Dietary supplement labeled dose is 0.13 g/kg/day

i. Discussion of Key Reproduction and Teratogenicity Studies on PSHusk and Relevance to PHC

• **SCOGS Report – Rat and Rabbit Reproductive Studies**

The SCOGS report reported that psyllium formulations in aqueous suspension were administered by gastric intubation at doses of 0.5 and 1.0 g/kg body weight (0.4 and 0.8 g/kg/day PHC) to 10 gravid Sprague-Dawley rats and 10 gravid New Zealand white rabbits on days 6 to 15 and 6 to 18 after conception respectively. Dosages of the “powder” formulation were 0.5 and 1.0 g/kg body weight and 0.5 g/kg body weight for the “instant dose” formulation. These doses respectively correspond to 0.4, 0.8, and 0.4 g/kg/day PHC. Necropsy of the rats on day 20 and the rabbits on day 30 of gestation revealed no significant differences between treated and control groups in the number of implantations or resorptions, or in number and weight of live fetuses. There were no dead or underdeveloped fetuses in the treated animals and no external, internal, or skeletal malformations found in the live fetuses.

• **Rabbit Reproductive Study**

Another study of PSHusk gum (*P.ovata*) in rabbits was conducted by Mercatelli and associates (1978). PSHusk gum (80% PHC) was administered by oral intubation 200 or 400 mg/kg of body weight/day (160 or 320 mg/kg/day PHC) as a mixture of the gum suspended in 1/3 v/v

water:polyethylene glycol 400). Test compound was administered from the 6th to 18th days of gestation; no deleterious effects were reported (Mercatelli et al., 1978).

- **Rat Two-Generation Reproductive and Teratology Study and a Rabbit Teratology Study**

In addition, P&G also conducted both a two-generation reproductive and teratology study in rats (Sutton, 1993; HPCR 0397) and a teratology study in rabbits (Wood, 1994; HPCR 0605) at Hazelton Laboratories, North America.

In the first study, male and female CrI:CD[®]BR VAF/Plus[®] rats nine weeks of age (30/sex/group) were fed diets containing 0 (basal diet), 0 supplemented with 5% avicel, or 1, 2.5, and 5 % psyllium (0.8, 2, 4% PHC) for 10 weeks throughout the F₀ and F₁ generations to assess the effect of psyllium on male and female mating performance and fertility; on the growth and development of the offspring from two consecutive generations; on gestation, parturition, lactation; and on fetal development and teratogenesis. Clinical observations, body weights, food and water consumption, and reproduction and litter data were recorded for the F₀ and F₁ generations. In addition, cesarean section data and fetal external, soft tissue, and skeletal examinations were done for the F_{2b} litters.

The only psyllium-related clinical observation during the F₀ and F₁ generations were non-formed feces. The mean body weights for males in the F₀ and F₁ generations consuming 5% psyllium (4% PHC) were generally lower than those of the control groups throughout pre-mating. Mean body weights for the F₀ and F₁ 5% psyllium-fed females were significantly higher than those of the control groups on Day 21 of lactation. With 2.5% dietary psyllium (2% PHC), the mean body weights for the males were generally lower than the basal diet controls throughout the F₁ generation. These differences were considered to be related to the dietary psyllium (PHC).

In the F₀ and F₁ generations, mean cumulative body weight changes for the 5% psyllium-fed (4% PHC) males were significantly lower than those of the control groups. Mean body weight gains for the 5% psyllium-fed (4% PHC) F₀ and F₁ generation females were higher than those of

the control groups during lactation. The differences in mean body weight changes were considered to be due to the dietary psyllium (PHC).

In the F₀ and F₁ generations, the significant differences in food consumption during pre-mating and post-mating for the males, and during pre-mating for the females were sporadic and not related to consumption of psyllium. During gestation, food consumption was generally higher for the 1%, 2.5%, and 5% psyllium-fed (0.8, 2, 4% PHC) F₀ and F₁ females than for the control groups. The increase in food consumption during gestation can be attributed to the ingestion of psyllium (PHC).

Water consumption was increased for the 2.5% and 5% psyllium-fed (2 and 4% PHC) F₀ males compared to the control groups throughout pre-mating. Significant differences in water consumption during pre-mating for the F₀ females were sporadic. In the F₁ generation, the water consumption for the 5% psyllium-fed (4% PHC) females was generally increased during pre-mating. During gestation and lactation, water consumption for the F₀ and F₁ females was generally higher than that of the control groups.

During lactation for both generations, the mean water consumption for the 2.5% and 5% psyllium-fed (2 and 4% PHC) females was significantly higher than that of the control groups. The increases in water consumption for the 2.5% and 5% (2 and 4% PHC) males and females were considered to be related to the dietary psyllium (containing 80% PHC).

There were no psyllium-related effects on reproductive performance, including mating performance and fertility. There were no significant differences in the sperm evaluation parameters. Pup weights were significantly reduced for the 2.5% and 5% psyllium-fed (2 and 4% PHC) groups in both generations. There were no psyllium-related (or PHC) effects on fetal development.

In the F₀ and F₁ generations, terminal body weights were significantly lower in males given 5% dietary psyllium (4% PHC) compared with males given the basal diet. No toxicologically important changes in absolute organ weights, organ-to-body weight percentages, or organ-to-brain weight ratios were observed. There were no PHC or psyllium-related macroscopic or histomorphologic changes in the F₀ or F₁ generations.

It can be concluded that when psyllium was administered to Crl:CD@BR rats continuously in the diet through two generations at concentrations as high as 5% (4% PHC), the no-observable-adverse effect levels were 5% (4% PHC) for mating performance and fertility, 1% (0.8% PHC) for offspring growth and development (based on reductions in pup weights at 2.5% and 5%), and 5% (4% PHC) for fetal development and teratogenesis.

The second study conducted by P&G (Wood, 1994; HPCR 0605) was a developmental toxicity study including assessing the teratogenic potential of psyllium when fed to pregnant rabbits before implantation and during organogenesis. Mated Hra:(NZW) SPF rabbits were received on either day 2, 3, or 4 of gestation and assigned at random to five groups of 20 animals each. Four groups received a basal diet of Purina Certified Rabbit diet #5322 to which psyllium was added at levels of 0%, 2.5%, 5.0%, or 10% (0, 2, 4, or 8% PHC). Purina Certified High Fiber Rabbit Diet #5325, used as a second control diet, was fed to another group. Animals received their respective diets on a restricted ration basis on the first day of receipt, and *ad libitum* thereafter through Day 29 of gestation. Clinical observations for mortality/morbidity were performed twice daily. Body weights were recorded on Gestation Days 0, 4, 7, 10, 13, 16, 20, 24, and 29. Food and water consumption were measured daily beginning on Gestation Day 4. Cesarean sections and necropsies were done on surviving animals on Gestation Day 29, and the fetuses were removed for external, visceral, and skeletal examinations.

The clinical observations that were related to ingestion of the psyllium and PHC were confined to fecal findings. Ingestion of the 10% psyllium-containing (8% PHC) diet resulted in lower mean body weights and body weight gains (including body weights and net body weight changes corrected for uterine weights). Mean food consumption of the groups that ingested the psyllium-

containing diets tended to be lower than that of both control groups during gestation, and were significantly lower for most intervals. Mean water consumption of the group consuming 10% dietary psyllium (8% PHC) was significantly lower than that of the control groups throughout gestation. The findings observed at necropsy among animals that received the dietary psyllium (80% PHC) were not considered to be related to treatment because of their low incidence.

Mean corpora lutea, implantation sites, total resorptions, and live fetuses of the groups that received the test materials were comparable to those of the control groups. There were no treatment related differences in the fetal sex ratios or mean fetal body weights of the psyllium-treated (PHC) groups. There were no abnormal fetal morphological findings that were considered related to psyllium (PHC) treatment. Fetal malformations and variations seen in the groups exposed to psyllium (PHC) throughout gestation were either low in incidence or were comparable with the findings seen in the control groups.

It can be concluded from this study that the no-observable-adverse-effect level for developmental toxicity is 10.0% (8% PHC) based on the lack of adverse fetal findings. However, ingestion of psyllium resulted in lower maternal body weights, lower body weight gains, and water consumption at the 10.0% (8% PHC) level, and abnormal fecal findings and lower food consumption at all dietary levels of psyllium tested.

f. Mutagenicity and Carcinogenicity

While no information is available on mutagenicity or carcinogenicity testing of psyllium (PSHusk) or PHC, there are a number of core studies that support its lack of carcinogenicity. There was no evidence of carcinogenicity seen in five carcinogenesis bioassays conducted by the National Toxicology Program in 1982 on related GRAS fibers (locust bean gum, tara gum, guar, carrageenan, and gum arabic). When comparing psyllium (or PHC) to related GRAS fibers, similar physiological actions are seen (e.g., guar and cholesterol lowering, laxation, modulation of glucose absorption). There is general recognition of the safety of related food fibers (guar,

carrageenan) for food use. Psyllium, and its main soluble fiber component PHC, have general recognition of safety by the medical and scientific community.

Comparisons between psyllium (with 80% PHC) and guar in the P&G 91-day study referenced above demonstrated similar physiological effects (GI morphology by light microscopy, intestinal weight increases, food and water consumption, body weight gain, etc.). Psyllium (with 80% PHC) and guar also produced similar intestinal effects based on results from a P&G 28-day morphometrics study.

The six-month dog study identified in the SCOGS report above, as well as the 25-week rat study, and the P&G 91-day subchronic toxicity study all indicate no significant toxicity or lesions seen for psyllium containing 80% PHC fed up to 0.6-4 g/kg/day, with the remaining insolubles assumed to be toxicologically neutral.

Finally, the history of extensive human exposure to psyllium-containing fiber supplements and drugs (over 70 years of use in the U.S.) and monitoring of drug adverse reactions has revealed no unforeseeable chronic toxicity or carcinogenicity concerns for psyllium or PHC. All of the information cited provides a reasonable basis to conclude that PHC is expected to be safe under the labeled conditions of use. PHC is the gel forming, viscous, main fraction (80%) of PSHusk responsible for its primary fiber benefits and physiological activity.

2. Summary of Animal Toxicology Data Pertinent to PHC

Since PHC makes up 80% of PSHusk, and the remaining insoluble material is poorly fermented and assumed to be toxicologically neutral based on expert opinion and studies on cellulosic materials, this leads to the conclusion that there is a reasonable expectation of a very good margin of safety at a daily use of PHC in dietary supplements at 7.5 g/day. Safety margins range from 1-30 depending on the study type, dose, and test substance. No effect levels are significantly higher than expected exposure from dietary supplement use.

The lack of any toxicological findings from any animal study on PSHusk and, by extension, its major component PHC allows the conclusion of safety for its recommended use. PHC is non-toxic in acute animal studies at a dose up to 4.8 grams/kg of body weight (6 g/kg PSHusk). There were no maternal, embryotoxic or teratogenic effects in a teratology study in rats or rabbits given up to 500 mg/kg psyllium (400 mg/kg PHC) over most of the gestational period. In several early subchronic feeding studies in rats and in a limited number of dogs, PSHusk (with 80% PHC) did not produce any adverse toxicological effects. These studies and the history of safe use of psyllium products containing 80% PHC clearly demonstrate the safety of PHC under expected conditions of dietary supplement use.

Section V

A. Consumer Research Tests on Psyllium Hemicellulose and Related Safety Information

This Notification does not deal with the truthfulness of potential claims of products containing PHC. This information is only provided as background to support the conclusion of PHC safety since the literature on PSHusk and cholesterol effects is extensive, and PSHusk safety and human exposure are well established at the levels referenced in the Soluble Fiber Health Claim Final Rule (7 grams soluble fiber/day).

An extensive number of PHC product research tests have been conducted at our research site and with consumers to assist in design of the commercial product. The primary purpose of these tests was to determine the level of consumer satisfaction with the sensory properties and fiber supplement qualities of the prototyped product. A summary of the number of people who participated in each test is presented in the Table 22 below.

In these studies, the product is coded with the name Marlett. The tests were conducted over a period of four years. PHC was tested in over 2400 subjects during this time period. Results of these studies are proprietary and not directly relevant to the safety determination of the dietary

ingredient, PHC. However, it is very important to note that the safety of PHC has been reaffirmed here, since no significant or serious adverse events attributed to PHC occurred during these tests, which in many cases involved prolonged exposure at the same levels planned for marketing (2.5 g/dose, 3 times per day). The low order of toxicity observed is very similar to that in the plethora of published work on PSHusk, which is reasonable given the fact that PHC is 80% of PSHusk.

Table 22 shows employee* and consumer usage of Marlett (Psyllium Hemicellulose) in PRT (Product Research Test) studies conducted December 2000 to December 2004. All research was carried out in the United States, under carefully administered informed consent and confidentiality documents.

Table 22
Research Tests with PHC Did Not Show Adverse Events

Study code	#	Marlett Usage* (full dose of 2.5 g PHC unless otherwise noted)	Calculated Daily Exposure (g/day)
EAS1	100	1 full single dose* once daily for 3 days	2.5
EAS2	100	1 full single dose once daily for 3 days	2.5
EAS4	100	1 full single dose once daily for 3 days	2.5
EAS5	100	5 full doses (1 a day for 5 days)	2.5
EAS6	100	1 full single dose once daily for 3 days	2.5
EAS8	120	1/3 of a single dose once only	0.8
EAS9	100	5 full doses (1 a day for 5 days)	2.5
Concept Fit (Baltimore)	20	Up to 3 x daily usage for up to 14 days	7.5
In Touch (Atlanta)**	40	Up to 3 x daily for up to 14 days	7.5
	24	1 partial dose only	2
Naming Study (multi-site US)	400	1 full single dose	2.5
In Touch Phoenix	32	Up to 3 x daily usage for up to 14 days	7.5

Study code	#	Marlett Usage* (full dose of 2.5 g PHC unless otherwise noted)	Calculated Daily Exposure (g/day)
Single Product Blind test	650	Up to 3 x daily for up to 14 days	7.5
Bases	380	Up to 3 x daily for up to 14 days	7.5

*Full single dose = 2.5 g PHC (Marlett)

**One transient and non-serious event was experienced in this "In-Touch" study; a female experienced itching of her skin and discontinued ingestion. The itching then resolved. No other unexpected or serious events were observed for the Marlett product in any of the other exposures.

1. Exposure Estimates for Psyllium Seed Husk in Food as It Relates to Psyllium Hemicellulose

The Federation of American Societies for Experimental Biology (FASEB) Life Science Research Office (LSRO) Expert Panel in 1993 prepared and agreed with a GRAS report which established that consumption of one food item containing PSHusk on a single serving occasion would result in mean intakes ranging from 1.9 to 5.3 grams per eating occasion for 1- to 2-year-old children and 4 to 12.1 grams for 15- to 18-year-old males. For the 90th percentile consumers, intakes would range from 3.8 to 11.0 grams per eating occasion for 1- to 2-year-olds and from 7.5 to 21.9 grams per eating occasion for 15- to 18-year-old males.

Further, on the basis of usual consumption, consumption of one item containing PSHusk would result in mean intakes of 0.7 to 2.7 grams/day for 1- to 2-year-old children and 1.3 to 5.4 grams/day for 15- to 18-year old males. For the 90th percentile consumers, PSHusk intake from one food item would range from 1.3 to 5.7 grams/day for 1-to 2-year old children and 2.7 to 11.3 grams/day for adolescent males.

These anticipated 90th percentile food GRAS (Generally Recognized as Safe) exposures of up to 22 g PSHusk greatly exceed expected exposure to the PHC dietary ingredient that is the subject of this Notification of up to 7.5g/day based on labeled use and 2.5 g/dose PHC. The highest level of 22 g PSHusk per day is equivalent to 19 g/day PHC, since PHC is 80% of PSHusk.

Since the 90th percentile adult consumption projection estimates for PSHusk raised no safety concerns from the LSRO GRAS Expert Panel, this strongly reinforces the conclusion regarding the basis for the safety of PHC, which will be used at less than half that level for dietary supplement use. For children ages 6-12, labeled PHC dietary supplement use would result in exposure of up to 3.5 g/day, compared to 90th percentile food PHC levels of up to ~10 g/day for that age group.

In their 1993 GRAS report, the LSRO Expert Panel noted that while total dietary fiber intake might increase slightly to 1-5 g/day from psyllium use in cereal products, some adults may preferentially consume psyllium products up to a maximum of 25 grams/day of PSHusk. This would equate to consumption of 21 grams/day of PHC from the PSHusk.

Since PHC comprises 80% of PSHusk as the soluble fiber component of PSHusk, this PSHusk review by LSRO in 1993 also supports the safety of PHC, as the 90th percentile intake levels are far above the adult labeled dosage of the PHC dietary supplement of 2.5 g/dose, taken up to 3 times per day. This represents a total adult dietary ingredient use of ~7.5 grams/day PHC compared to 21 g/day calculated from food use of PSHusk which contains PHC.

The information and conclusions from this LSRO GRAS assessment for PSHusk (which is 80% PHC) and related psyllium ingredients support the conclusion that PHC is reasonably expected to be safe at the labeled usage condition specified in this Notification. This conclusion is based on the assumption that removal of the insoluble fraction from PSHusk during extraction of PHC does not affect the safety profile of the major component, so the PSHusk safety studies and

GRAS conclusions apply to PHC, when exposure levels are adjusted for the 80% composition factor.

2. Side Effects/Toxicity

No adverse effects of clinical significance from consuming psyllium seed or husk have been reported in clinical studies. These studies are directly applicable to PHC because PHC is 80% of PSHusk, and the removal of ~20% insoluble fraction via extraction may be expected to only decrease risk of allergenicity due to presence of higher levels of protein in PSHusk (1.9%) vs. PHC (0.5%). There were also no changes reported in vitamin or mineral content in any of the studies referenced above. A 52-week study by Oliver, (2000) of 93 healthy individuals reported small but statistically significant changes in some measurements of mineral and vitamin levels and in some hematological and biochemical parameters. None of these were of clinical significance except for very minor changes in vitamin B₁₂ levels. As noted by the Expert FASEB GRAS Panel in 1993, there are no anecdotal or clinical observations of possible effects on vitamin or mineral absorption or metabolism from a long history of use of psyllium-containing laxatives. Subsequent studies on PSHusk and PHC have confirmed no new or significant adverse effects in studies conducted since the FASEB report.

3. Adverse Effects/Contraindications

Several cases of allergy, hypersensitivity, anaphylaxis, choking due to esophageal blockage from granular forms, and asthma have been reported in the psyllium safety literature, so caution must be exercised in allergy-prone individuals and those with difficulty swallowing. The majority of the allergic responses reported to date have been due to occupational exposure and continuous handling of powdered product. Khalili et al. (2003) provide a recent case report and review of the literature. To avoid these issues for PHC, which are the same as for PSHusk, we plan to use the same type of labeling, which is described in an earlier section.

Section VI

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SECTION VII

A. Appendix A

Sample Calculations for Normalization of Animal Studies- for Summary Tables of PHC Test Dose in Section IV

For reference #3.

Rats consume 5% of their body weight in feed each day.¹

The exposure was 8% PHC in feed.

$$(8 \text{ g PHC} / 100 \text{ g feed}) \times (5 \text{ g feed} / 100 \text{ g body weight}) \times (1000 \text{ g body weight} / 1 \text{ kg body weight}) = 4 \text{ g/kg/day}$$

For reference #10.

Monkeys consume 2% to 4 % of their body weight in feed each day.² The lower end of the range, 2%, will be used.

The exposure was 7.8% PHC in feed.

$$(7.8 \text{ g PHC} / 100 \text{ g feed}) \times (2 \text{ g feed} / 100 \text{ g body weight}) \times (1000 \text{ g body weight} / 1 \text{ kg body weight}) = 1.5 \text{ g/kg/day}$$

¹These values represent conservative defaults used historically by USEPA for use in converting dose metrics from chronic toxicity studies [USEPA. 1985. Reference Values for Risk Assessment. Prepared by the Office of Human and Environmental Assessment; Environmental Criteria and Assessment Office; Cincinnati, OH for the Office of Solid Waste, Washington, DC].

²LabDiet Product Reference Manual: Certified Primate Diet. PMI Nutritional International. Accessed 23-FEB-2006. <www.labdiet.com>

B. Appendix B

Studies Which Support the Safety of the NDI Substance- Psyllium Hemicellulose

The studies included in the main body of the NDI document are all considered pivotal to the safety determination, since the exposure level of PHC in the psyllium test material could be quantified and compared to the intended exposure to the NDI substance. The PHC level documented in the Safety Section tables for each of these tests was based on documentation in the reports or publications of either analysis or a clear description of the test substance. As discussed earlier, a consistent ratio of PHC in PSHusk of ~80% was found via both analytical and soluble fiber comparisons.

In contrast, the exact amount of PHC used in the two following subchronic studies is difficult to quantify based on the data provided, because the amount of PHC in the test substances has not been quantified in the same way as for PSHusk. Therefore we regard these two studies as supportive of the safety of PSHusk and supportive of the overall safety profile of PHC.

The test substances used in these two studies are blond psyllium seed powder and whole psyllium. The SCOGS report discusses a 14-day study in rats conducted by Ershoff (1977) whereby the effects of addition of 10% blond psyllium seed powder, carrot root powder, alfalfa leaf meal or wheat bran to low fiber purified diets containing 5% tartrazine (FD&C Yellow No.5) or Sunset Yellow FCF (FD&C Yellow No.6) was examined. Blond psyllium seed powder is higher in protein than typical PSHusk and may be reduced in PHC level compared with husk. An estimate of PHC exposure from this study is 4-7% PHC. Weight gains, general appearance, and mortality rates of the groups fed the food dyes were improved when psyllium seed powder, carrot root powder, alfalfa leaf meal, or wheat bran was incorporated into the diet. The author (Ershoff) did not identify which of these substances (if any) was responsible for the improvements in weight gain, appearance, and mortality rates, but speculated on several possible mechanisms of action.

Additional subchronic studies were discussed in the SCOGS report. Rats fed diets containing 25% *Plantago* psyllium for 125 days showed fine brown granules in the epithelial cells of the kidney tubules (Mackay, 1932). The author attributed this to a pigment from the PSHusk and this same event was not seen in dogs fed diets containing 25% *Plantago* psyllium for 30 days (Mackay, 1932). The material tested in this study also appears to be whole seed, not PSHusk, which again, would have a reduced PHC level. The PHC level tested in this study may range from 10-18% PHC.

While the exact PHC exposure level is uncertain in both studies since they do not test PSHusk, which is 80% PHC, both of these studies are supportive of PHC safety.