The Quaker Oats Company, 617 Main Street, Barrington, Illinois 60010 (847) 381-1980

April 12, 2001

Lynn A. Larsen, Ph.D.
Director, Div. of Nutrition Science & Policy
Office of Nutrition Products, Labeling and
Dietary Supplements
Center for Food Safety & Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

Dear Dr. Larsen:

As requested, The Quaker Oats Company and Rhodia Inc., are hereby submitting an additional copy of the Oatrim (BetaTrim™) petition to expand the original health claim concerning the relationship between the consumption of soluble fiber from certain foods and reduced coronary heart disease (CHD). The current petition requests that 21 CFR 101.81 be expanded to include Oatrim, with specific reference to the Quaker-Rhodia group of Oatrim, known as BetaTrim™.
The enclosed includes the following information:

- Overall evidence that demonstrates our fulfillment of the health claim requirements set forth in 21 CFR 101.14 to permit a health claim for the relationship between Oatrim (BetaTrim™) and CHD.
- A PAPER copy of the *original petition* dated April 05,2001
  This is a summary of scientific evidence demonstrating the cholesterol-lowering efficacy of Oatrim (BetaTrim™)
- A second set of scientific articles/references & appendices (2 binders)
- A third COPY of the petition, references and appendices 6 & 7 in electronic form (CD-rom).

Should the U.S. Food and Drug Administration (FDA) grant preliminary approval of this health claim petition, Quaker Oats and Rhodia also request that FDA grant an *Interim Final Rule* by which products containing Oatrim (BetaTrim™) could carry the "Oats/soluble fiber and CHD health claim" during the period after FDA's preliminary approval and prior to its publication of a Final Rule.

01Q-0313

HCN1

Again, please do not hesitate to contact Quaker Oats or Rhodia if further discussion or information is required. For this reason, questions, phone calls, and communication may be addressed to the undersigned at the address provided.

Thank you.

Yours truly,

Priscilla Samuel, Ph.D.
Senior Scientist
Director, Clinical Research Programs
(847) 304 2230

Mark L. McGowan
Counsel
The Quaker Oats Company
(312) 222 7801

The Quaker Oats Company, 617 Main Street, Barrington, Illinois 60010 (847) 381-1980

April 5, 2001

Lynn A. Larsen, Ph.D.
Director, Div. of Nutrition Science & Policy
Office of Nutrition Products, Labeling and
Dietary Supplements
Center for Food Safety & Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204

Dear Dr. Larsen:

The Quaker Oats Company and Rhodia Inc., are hereby submitting a petition to expand the original health claim concerning the relationship between the consumption of soluble fiber from certain foods and reduced coronary heart disease (CHD). The current petition requests that 21 CFR 101.81 be expanded to include Oatrim, with specific reference to the Quaker-Rhodia group of Oatrim, known as BetaTrim™.

The enclosed petition and binders (2) contain the following information:

- Summary of scientific evidence demonstrating the cholesterol lowering efficacy of Oatrim (BetaTrim™)
- Evidence that demonstrates our fulfillment of the health claim requirements set forth in 21 CFR 101.14 to permit a health claim for the relationship between Oatrim (BetaTrim™) and CHD.

Should the U.S. Food and Drug Administration (FDA) grant preliminary approval of this health claim petition, Quaker Oats and Rhodia also request that FDA grant an *Interim Final Rule*, by which products containing Oatrim (BetaTrim) could carry the "Oats/soluble fiber and CHD health claim" during the period after FDA's preliminary approval and prior to its publication of a Final Rule.

Please do not hesitate to contact Quaker Oats or Rhodia if further discussion or information is required. For this reason, questions, phone calls and communication may be addressed to the undersigned at the address provided.

Yours truly,

Priscilla Samuel, Ph.D.
Senior Scientist
Director, Clinical Research Programs
(847) 304 2230

Mark L. McGowan
Counsel
The Quaker Oats Company
(312) 222 7801

Encl: Petition
Reference Binders (2)

DATE: April 5, 2001

OFFICE OF NUTRITION PRODUCTS, LABELING AND DIETARY SUPPLEMENTS
CENTER FOR FOOD SAFETY & APPLIED NUTRITION
FOOD AND DRUG ADMINISTRATION
200 C STREET SW
WASHINGTON, DC 20204

PETITIONERS: **The Quaker Oats Company**
617 W. Main Street
Barrington, IL 60010
&
Rhodia Inc.
CN 7500, 259 Prospect Plains Road
Cranbury, NJ 08512-7500

SUBJECT: **OATRIM (BETATRIM™) HEALTH CLAIM PETITION**

Petition to Expand the Oats Soluble Fiber and Coronary Heart Disease Health Claim, (21 CFR 101.81)

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I. INTRODUCTION

A. OVERVIEW OF PROPOSAL

The Quaker Oats Company (Quaker Oats) and Rhodia Inc., pursuant to section 403 (r)(4) of the Federal Food, Drug, and Cosmetic Act, submit this health claim petition concerning the relationship between the consumption of soluble fiber from certain foods and reduced coronary heart disease (CHD) risk. This petition requests that the "Soluble Fiber from Certain Foods and Coronary Heart Disease Health Claim" (21 CFR 101.81) be expanded to include Oatrim[1], with specific reference to the Quaker-Rhodia group of Oatrim, known as Oatrim (BetaTrim™)[2]. Oatrims are concentrated sources of oat β-glucan soluble fiber made from whole oat flour or oat bran.

Not all Oatrims have been tested for cholesterol-lowering efficacy; hence we are limiting our petition to the subgroup of Oatrim (BetaTrim™), Oatrims with demonstrated cholesterol-lowering efficacy. The BetaTrim™ designation in parenthesis allows the subject subgroup to be distinguished from other Oatrims that have not demonstrated cholesterol-lowering efficacy and have not been approved to use the soluble fiber and CHD health claim. The subgroup Oatrim (BetaTrim™) has a β-glucan content of 4% to 25% and is manufactured by one of two controlled hydrolysis processes—an acid/base method or an enzymatic method as described in Appendices 1A and 1B. The remainder of this document will refer to this subgroup as Oatrim (BetaTrim™).

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[1]Oatrim: Common or usual name for a class of food ingredients which are sources of oat β-glucan soluble fiber and oat starch obtained by enzymatic and/or acid-base hydrolysis of whole oat flour or oat bran. The β-glucan soluble fiber concentration of Oatrim is often specified for example as Oatrim-5 or Oatrim-10 – equivalent to 5% and 10% β-glucan. Historically, for labeling purposes, this ingredient was originally declared as hydrolyzed oat flour or hydrolyzed oat bran. More recently the term "Oatrim" has been used as the common or usual name. In the scientific literature Oatrim is often referred to as oat bran concentrate but has also been described by a couple of researchers as "oat extract" (However, note that purified oat extract and oat gums are described and defined differently in this petition).

[2]Oatrim (BetaTrim™): A specific group of Oatrim developed by The Quaker-Rhodia Partnership, using two controlled processes (acid/base & enzymatic hydrolysis processes described in Appendix 1A & B) containing a β-glucan soluble fiber concentration ranging from 4% to 25% and with demonstrated cholesterol-lowering efficacy. This group of Oatrim are commercially available under the brand-name BetaTrim™ and include, Oatrim (BetaTrim™) –5, -10, and –20, containing β-glucan levels of approximately 5%, 10%, and 20%, respectively.

Evidence detailed in this petition shows that Oatrim (BetaTrim™) is efficacious in lowering serum cholesterol and thereby has the potential to reduce CHD risk. Processed oat β-glucan soluble fibers with significantly higher β-glucan content (i.e. approximately 60-80%) such as oat gums and oat extracts have also been shown to have cholesterol-lowering efficacy in human clinical trials. However, they are not the focus of this petition. Quaker Oats and Rhodia Inc. believe that we have fulfilled the health claim requirements set forth in 21 CFR 101.14 to permit a health claim for the relationship between Oatrim (BetaTrim™) and CHD. Consistent with the soluble fiber health claim (21 CFR 101.81), we propose that 3 g of β-glucan soluble fiber per day be required as the amount needed to make a significant impact on serum lipid levels, with Oatrim (BetaTrim™) providing 0.75 g β-glucan soluble fiber per reference amount customarily consumed to the food that is eligible to bear the claim.

Human and animal studies have shown that the β-glucan from Oatrim (BetaTrim™) has sufficient efficacy to lower cholesterol. Animal studies have also shown that Oatrim (BetaTrim™) has supernatant intestinal viscosities similar to or greater than rolled oats and oat bran[3]. FDA has supported the view that *in vivo* viscosity of intestinal contents demonstrated in animals is a critical factor in establishing cholesterol-lowering potential (62 FR 3586, Jan. 23, 1997).

Quaker and Rhodia propose that 21 CFR 101.81 be changed to include Oatrim (BetaTrim™) as a source of β-glucan soluble fiber from oats eligible to be the substance in the health claim. We believe that the incorporation of Oatrim (BetaTrim™) in a variety of foods will provide consumers with a wider degree of choice in obtaining β-glucan soluble fiber foods and subsequently a greater opportunity to lower serum cholesterol levels and CHD risk.

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[3]Supernatant intestinal viscosity (*in vivo*): A measure of the supernatant viscosity of small intestine contents after animals have been meal-fed or chronically-fed a test substance. Intestinal contents are centrifuged and resistance to flow of the particulate-free supernatant is measured using a Viscometer. See Gallaher et al, 1999 for more details on this method.

B. BACKGROUND

In 1997, the Food and Drug Administration (FDA) approved the health claim on the association of soluble fiber from rolled oats and reduced risk of heart disease (21 CFR 101.81) (62 FR 3584, January 23, 1997). FDA was persuaded that β-glucan soluble fiber was the primary component of whole oat products in affecting serum lipids. The agency stated that β-glucan soluble fiber plays a significant role in the relationship between whole grain oats and the risk of coronary heart disease (CHD). This conclusion was based on two major findings from the evidence reviewed. There was a dose response between the level of β-glucan soluble fiber consumed and the level of reduction in blood total- and LDL-cholesterol. Beta-glucan intakes of 3 g or more per day were effective in lowering serum lipids.

Rolled oats (i.e. whole oats) and oat bran were the subjects of Quaker Oats' original health claim petition, however in the final rule (62 FR 3585-6, January 23, 1997), whole oat flour was included as an oat product eligible to bear the claim. FDA reviewed the evidence and comments submitted to support the inclusion of whole oat flour and noted the following:

i) "In considering the comments concerning the inclusion of whole oat flour in this rulemaking, the agency has reviewed the evidence referenced in these comments, including the additional data submitted. **The agency noted the similarity of whole oat flour to rolled oats in terms of chemical and physical properties and type of processing.** After careful consideration of the scientific evidence and the nature of the proposed health claim, FDA has concluded that products made with whole oat flour from 100 percent oat groats should be eligible to bear a claim." (62 FR 3586, Jan. 23, 1997; Section II3)

ii) "**These results** (*in reference to the human study submitted*) **are consistent with the findings for oat bran and rolled oats,** i.e., positive effects on blood total- and LDL-cholesterol levels in mildly hypercholesterolemic subjects adhering to a diet low in saturated fat and cholesterol. Therefore, this study, along with evidence submitted by comments showing compositional similarities between

whole oat flour and rolled oats, provides sufficient evidence for the agency to conclude that whole oat flour has the same effects relative to reduced risk of CHD as do oat bran and rolled oats." (62 FR 3586, Jan. 23, 1997; Section II3).

iii) "**Further, there is evidence that corroborates this conclusion that is provided by animal studies. These animal studies addressed the issue of retention of viscosity characteristics during processing and digestion.** Because viscosity of intestinal contents is known to be a critical factor in determining the ability of soluble fibers to reduce the risk of CHD and because viscosity is known to be affected by food processing procedures or, following ingestion, by the digestive system in ways that are unpredictable, evidence to demonstrate that the β-glucan soluble fiber from whole oat flour retains the same level of viscosity in the digestive tract as does that from rolled oats is crucial to the question of whether whole oat flour can provide the same benefits as rolled oats." (62 FR 3586, Jan. 23, 1997; Section II3).

iv) "**The animal studies cited by one comment demonstrate that there is bioequivalence relative to these important physical characteristics between whole oat flour and rolled oats.** When taken together, the available evidence provides a basis for concluding that it is appropriate to make whole oat flour, as well as oat bran and rolled oats, the subject of the authorized substance-disease relationship." (62 FR 3586, Jan. 23, 1997; Section II3).

Within the oats and CHD final rule Federal Register notice, FDA recognized that other sources of β-glucan soluble fiber, in addition to rolled oats, oat bran, and whole oat flour have the potential to affect blood cholesterol levels. However other sources of β-glucan soluble fiber were not considered eligible sources at the time the health claim was approved, because only the evidence for rolled oats, oat bran and whole oat flour was submitted and examined. FDA noted that it anticipates receiving future petitions for other sources of β-glucan soluble fiber to be added as subjects of the health claim.

FDA has suggested that manufacturers may petition to amend 21 CFR 101.81 to include other soluble fiber sources (e.g., processed or purified β-glucan soluble fibers, oat gums or other non-oat sources) (62 FR 3584, January 23, 1997) (63 FR 8103, February 18, 1998). Following Quaker Oats' health claim petition for oats and CHD, the Kellogg Company filed a health claim petition for the association between soluble fiber from psyllium seed husk and CHD. In 1998, FDA amended the regulation that authorized a health claim on soluble fiber from rolled oats and the risk of CHD (21 CFR 101.81) to include soluble fiber from psyllium husks (63 FR 8103, February 18, 1998). Due to the heterogeneous nature of soluble fiber sources and the variability of their impact on CHD risk, FDA stated that it is necessary to evaluate each source on a case-by-case basis by providing adequate documentation that the soluble fiber source has an effect on blood total- and LDL-cholesterol levels and therefore is useful in reducing risk of CHD.

In 1992, Quaker and Rhodia entered into a partnership to commercially produce and market Oatrim (BetaTrim™) for use in various food products. Oatrim (BetaTrim™) containing food products have been safely consumed by the public for a number of years, including but not limited to cereals, frozen foods, dairy products, beverages, baked products, mixes, and meat and poultry products.

The information in this petition demonstrates that, Oatrim (BetaTrim™) meets all the eligibility requirements for a health claim in 21 CFR 101.14(b). Additionally, Oatrim (BetaTrim™) meets and exceeds all of the criteria considered by FDA in including whole oat flour in the health claim. The β-glucan soluble fiber in Oatrim (BetaTrim™) is the same as that found in oat bran, rolled oats, and whole oat flour. Oatrim (BetaTrim™) is derived from the same starting materials as oat bran and whole oat flour. Animal viscosity studies demonstrate that the β-glucan in Oatrim (BetaTrim™) retains many of the physiological characteristics of oat bran, rolled oats, and whole oat flour. Human and animal studies show that the β-glucan in Oatrim (BetaTrim™) retains its serum lipid-lowering efficacy.

II. PRELIMINARY REQUIREMENTS

C. OATRIM (BETATRIM™) IS ASSOCIATED WITH REDUCED RISK OF CORONARY HEART DISEASE, A DISEASE FOR WHICH THE U.S. POPULATION IS AT RISK [(21 CFR 101.14(b)(i)].

Although death rates from coronary heart disease (CHD) are declining, CHD is still the number one cause of death in the United States (CDC, 1999). CHD is also a source of lost productivity and substantial morbidity in the form of non-fatal myocardial infarction and angina (AHA, 1999). Elevated total cholesterol and LDL-cholesterol are well established as major modifiable risk factors for CHD (NCEP, 1993). It is also estimated that on a population basis for every 1% reduction in serum cholesterol, a 2-3% reduction in CHD is observed (NCEP, 1993).

It is estimated that 20% of American adults have high total blood cholesterol (240 mg/dL and above), and an additional 31% have borderline risk levels (Sempos et al, 1993). According to data from The Third National Health and Nutrition Examination Survey (NHANES III), 65% of all American adults aged 40 years and older have a borderline risk serum cholesterol level, between 200 and 239 mg/dL (Samuel et al, 2000). Must et al (1999), also using NHANES III data, reported that more than half of all American adults are overweight or obese and that they were more likely to have high blood cholesterol levels than normal weight individuals. This obesity trend is growing in epidemic proportions globally and is also an independent risk factor for CHD. According to the National Heart, Lung and Blood Institute (NHLBI, 2000), CHD accounts for almost two thirds of all heart disease related deaths in the U.S. These data establish the fact that within certain segments of the U.S. population, more than half the population is at risk for CHD.

Dietary approaches to reducing blood cholesterol levels have been shown to reduce the risk of CHD both at the individual and at the population level. Dietary fiber, especially soluble fiber, has been well established as a means of reducing serum total- and -LDL cholesterol levels. However, the mean total dietary fiber intake for the total U.S. population two years and older is only 16 g/day (Appendix 2), which is far below the generally recommended 25-

30 g/day. The effectiveness of soluble fiber is dependent on consuming a sufficient quantity of β-glucan and other soluble fibers over a period of time. Incorporation of Oatrim (BetaTrim™) into a variety of foods will provide consumers a greater opportunity to both increase their total soluble fiber intake as well as reduce CHD risk.

Oatrim (BetaTrim™), as a source of oat β-glucan soluble fiber has been demonstrated to significantly reduce serum total- and LDL- cholesterol in both human and animal studies (see Section III A–C: Summary of Scientific Evidence). Therefore, Oatrim (BetaTrim™) can contribute to the reduction of CHD risk in the U.S. population.

B. OATRIM (BETATRIM™) IS A FOOD INGREDIENT THAT PROVIDES NUTRITIVE VALUE AND TECHNICAL EFFECTS [21 CFR 101.14 (b)(3)(i)]

Oatrim (BetaTrim™) is the focus of this petition. It belongs to a class of food ingredients known as Oatrims, which are concentrated sources of oat β-glucan soluble fiber made from whole oat flour or oat bran. Not all Oatrims have been tested for cholesterol-lowering efficacy; hence we are limiting our petition to the subgroup Oatrim (BetaTrim™), Oatrims with demonstrated cholesterol-lowering efficacy. The sub-group of Oatrim known as BetaTrim™ has a β-glucan content of 4% to 25% and is manufactured with one of two controlled hydrolysis processes—an acid/base method or an enzymatic method as described in Appendices 1A & B. The BetaTrim™ designation in parenthesis allows the subject subgroup to be distinguished from other Oatrims that have not demonstrated cholesterol-lowering efficacy and have not been approved to use the soluble fiber and CHD health claim.

Oatrim (BetaTrim™) has nutritive value in that it provides energy and is a concentrated source of β-glucan soluble fiber. Depending on the β-glucan soluble fiber concentration of the starting material (whole oat flour or oat bran), the resulting Oatrim (BetaTrim™) product can vary in β-glucan soluble fiber concentration. Table 1 summarizes the macronutrient composition of three Oatrim (BetaTrim™) ingredients with a β-glucan concentration ranging from 4% to 25%. The manufacturing process removes most, but not all of the oat lipid, protein and insoluble fiber fractions, resulting in a product that is primarily a carbohydrate

and β-glucan soluble fiber source. In its nutritional profile, Oatrim (BetaTrim™) is similar but not identical to rolled oats, oat bran and whole oat flour. Table 2 summarizes some of the physical and chemical features of Oatrim (BetaTrim™). Oatrim (BetaTrim™) contributes several technical effects (e.g., as a water-binder, humectant and/or texture modifier) that are retained when it is consumed at levels necessary to justify the petitioned claim. Oatrim (BetaTrim™) also has demonstrated cholesterol-lowering efficacy. It is a food ingredient that has been historically consumed and exists in foods such as low-fat pancakes, muffins, cookies, biscuits, nutrition bars, fat-free frankfurters, candy, dairy products and beverages. Oatrim (BetaTrim™) (4 – 25% oat β-glucan) therefore satisfies the preliminary requirement of the regulation in §101.14(b)(3)(i).

On the basis of FDA's guidelines [21 CFR 101.14 (b)(3)(i)], it can be concluded that Oatrim (BetaTrim™) provides nutritive value and technical function and therefore satisfies the preliminary requirements for the following reasons:

i) Oatrim (BetaTrim™) is a source of energy and a concentrated source of an essential nutrient, soluble fiber.

ii) Oatrim (BetaTrim™) lowers serum cholesterol levels, and therefore when consumed as part of a total diet, may reduce the risk of CHD.

iii) Oatrim (BetaTrim™) is a source of oat β-glucan soluble fiber, the same substance that has been recognized in oat bran, rolled oats, and whole oat flour to lower CHD risk.

Table 1. Typical Macronutrient Composition of the Oatrim (BetaTrim™) Sub-Group, Rolled Oats, Oat Bran, and Whole Oat Flour (Per 100g)

Nutrient	Oatrim (BetaTrim™-5)	Oatrim (BetaTrim™-20) (Enzyme)	Oatrim (BetaTrim™-20) (Acid/Base)	Rolled Oats	Oat Bran	Whole Oat Flour
Calories (kcal)	337	367	336	389	397	384
Calories from fat (kcal)	6.3	13.5	56	62.1	63.3	62.1
Total Fat (g)	0.7	1.5	6.2	6.9	7.0	6.9
Saturated Fat (g)	0.3	0	0	1.2	1.3	1.3
Cholesterol (mg)	0	0	0	0	0	0
Total Carbohydrate (g)	89.6	84.9	51.2	66.2	66.2	67.3
Dietary Fiber (g)	6.2	25.7	28.6	10.3	15.9	10.5
β-glucan (g)	4.0 - 6.0	18-22	18-22	5	7.7	4
Protein (g)	1.5	3.5	18.9	16.9	17.3	13.7

Table 2. Physical and Chemical Features of Oatrim (BetaTrim™)

Characteristic	Oatrim (BetaTrim™)
Physical Form	Free-flowing cream colored powder that may be used as is or prepared as a gel
Molecular Structure of Mixed Beta-Glucan	30% (1-3) and 70% (1-4) beta-linkages
Molecular Weight	300,000- 2,000,000 g/mol
Components Used in the Processing of Oatrim (BetaTrim™)	Whole oat flour or Oat bran, Sodium Hydroxide, Phosphoric Acid, Calcium Chloride, Alpha- Amylase

C. OATRIM (BETATRIM™) IS SAFE AND LAWFUL [21 CFR 101.14 (b)(3)(ii)]

The safe and lawful use of Oatrim (BetaTrim™) has been established. Oatrim (BetaTrim™) is GRAS (generally recognized as safe) by self-GRAS determination by the Quaker Oats Company (1992; see Appendix 3). Oatrim (BetaTrim™) is derived from GRAS products, either oat bran or whole oat flour, which have been subjected to hydrolysis by treatment with safe and suitable food grade enzymes and/or GRAS listed food grade acids or bases.

Oatrim was first developed in the late 1980s as a fat replacer by George Inglett, a chemist at the USDA National Center for Agricultural Utilization Research. The USDA-patented ingredient had been licensed to ConAgra, Quaker Oats, and Rhodia Inc (then Rhone-Poulenc). In 1991, Quaker Oats and Rhodia Inc. joined forces to develop Oatrim (BetaTrim™). Oatrim (BetaTrim™) is an improved version of the original Oatrim with a neutral flavor, allowing Oatrim (BetaTrim™) to be incorporated into a number of foods. Over the last several years, Quaker Oats and Rhodia have sold Oatrim (BetaTrim™) (also known as Oatrim-5) with a concentration of 4-6% β-glucan soluble fiber, which has been incorporated by food manufacturers into a number of foods, including low-fat pancakes; muffins; biscuits; a low-fat, high-fiber-nutrition bar; and fat-free frankfurters.

Protient, Inc. sells Oatrim (the business was acquired from ConAgra) under the trade name of TrimChoice. Several of ConAgra's Healthy Choice products such as hot dogs, bologna, 96% fat-free ground beef, and cheese have used Oatrim-TrimChoice. Other smaller food manufacturers are using Oatrim in various products such as, muffins, cookies, chocolate candy, dairy products, beverages, frozen foods and prepared meats.

ConAgra also determined GRAS status of their Oatrim products in March 1991, through the use of an Expert Panel and an independent Self-GRAS determination (see Appendix 4, Consensus Statement by ConAgra Expert Panel, 03/22/91). In 1991, ConAgra also met with FDA officials to review its independent GRAS assessment of Oatrim and to review products containing up to 15% β-glucan soluble fiber (Oatrims-1,-5, &-10). Thereafter, ConAgra and The Quaker-Rhodia Partnership, have commercially produced and marketed Oatrim for use in various food products for several years. These food products have been safely consumed

by the public for a number of years, including but not limited to cereals, frozen foods, dairy products, beverages, baked products, mixes, and meat and poultry products.

An opinion letter concerning the GRAS status of oat β-glucan soluble fibers and purified forms at concentrations up to 25% β-glucan soluble fiber is provided in Appendix 5. The letter is written by Dr. Joseph F. Borzelleca, a well-renowned expert in toxicology and well versed in matters of GRAS. He states:

> "Beta-glucan soluble fiber is naturally occurring. Products containing beta-glucan soluble fiber have been consumed for a number of years without evidence of adverse effects. There is no reported toxicity at grams/kg body weight doses. The stool-softening effects of soluble fibers are well known and desirable".
>
> "...it is concluded that beta glucan soluble fiber produced and used in accordance with current Good Manufacturing Practices and meeting the specifications described, is GRAS for use as a water-binder, humectant, or texture modifier and as a source of β-glucan soluble fiber at concentrations up to 25% in various products".

The use of Oatrim, including Oatrim (BetaTrim™), hydrolyzed oat bran, and hydrolyzed oat flour in food products is widely accepted. As an example, USDA identifies these products in its product specifications for certain low fat bakery mixes it purchases for use in its domestic food assistance programs. USDA has also authorized these products in proprietary mix approvals for use in meat and poultry products. Therefore, the safe and lawful uses of Oatrim, including Oatrim (BetaTrim™), have been well established.

III. SUMMARY OF SCIENTIFIC EVIDENCE

A. OVERVIEW OF SCIENTIFIC DATA

In this section, both published and unpublished data will be reviewed and will demonstrate the bioequivalence of the β-glucan from Oatrim (BetaTrim™) to β-glucan from rolled oats, whole oat flour and oat bran. It will also be demonstrated that some processed β-glucan soluble fibers [including Oatrim (BetaTrim™)] significantly reduce total- and LDL-cholesterol. Using *in vivo* intestinal contents supernatant viscosity as a marker for the cholesterol-lowering capacity of foods, the animal data will demonstrate that the intestinal viscosity of Oatrim (BetaTrim™) is sufficient to lower cholesterol and that intestinal viscosity increases from low to high, respectively, with increasing concentrations of Oatrim (BetaTrim™) (i.e. 4, 12, or 20% β-glucan). Furthermore, the data will also indicate a dose response reduction of liver cholesterol, with the highest reduction observed with the 20% β-glucan Oatrim (BetaTrim™). Oatrim (BetaTrim™) ingredients processed either by enzymatic or acid/base methods do not differ in their impact on blood cholesterol. The human data will demonstrate that consumption of 1.6 g to 9 g of β-glucan soluble fiber from Oatrim sources produces significant reductions in blood total- and LDL- cholesterol levels of 9.2-14.8% and 10-23%, respectively.

> "Significant scientific agreement" has been established for the effectiveness of β-glucan soluble fiber from oats through multiple, peer reviewed, published clinical studies, and the approved Soluble Fiber and CHD Health Claim".

Overall, based on these data, it is evident that the 3 g of oat-β-glucan soluble fiber from Oatrim (BetaTrim™) would be adequate to significantly reduce total- and LDL- cholesterol, the effective level that has been evidenced and documented for β-glucan from rolled oats, oat bran and whole oat flour. Therefore, the consumption of Oatrim (BetaTrim™) can have a significant impact on the risk of CHD and public health of the U.S. population.

B. HUMAN CLINICAL DATA

1. Review of Human Studies (Appendix 6)

One human clinical study has evaluated Oatrim (BetaTrim™), the Quaker-Rhodia brand of Oatrim and a ConAgra brand of Oatrim (Behall et al, 1997; USDA-ARS, 1996). Both the Quaker-Rhodia and ConAgra brands of Oatrim used in this study were developed and processed with enzymatic methods licensed from George Inglett. The two Oatrim sources used in this study, represented "high" (Oatrim-10, 10.2% β-glucan) and "low" (Oatrim-1, 1.6% β-glucan) oat β-glucan levels[4]. In this study subjects were fed a "typical" maintenance diet for 1 week followed by diets containing foods with either the "high" or "low" Oatrim for 5 weeks in a crossover study design. The Oatrim replaced 5% of the energy from the maintenance diet. The maintenance diet provided 0.8 g of β-glucan, prior to the addition of the 50 g to 75 g of oat product ("oat extracts"). Approximately 0.8-1.2 g of oat β-glucan was added to the Oatrim-1 diet (resulting in 1.6-2.1 g of β-glucan per day) and 5.1-7.6 g of β-glucan was added to the Oatrim-10 diet (resulting in 5.9-8.4 g β-glucan per day). Total cholesterol and LDL-cholesterol was reduced by 9.5% ($p < 0.0001$) and 14.6% ($p < 0.0001$), respectively with the low β-glucan diet and 14.8% ($p < 0.0001$) and 20.8% ($p < 0.0001$), respectively with the high β-glucan diet.

The subjects in this study lost 1-1.7 kg during the oat phases. However, weight was not significantly associated with total- or LDL-cholesterol. Dietary changes were also assessed to determine its potential effect on serum cholesterol changes. There was a 5% difference in total fat intake between the maintenance diet (35% of calories) and the oat diets (30% of calories). Using the Keys equation, total serum cholesterol changes attributed to the lower fat intake were less than 8%, and during both oat phases serum cholesterol reductions were greater than 8%. Thus changes in fat intake were only partly responsible for the effect.

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[4] At the time this study was conducted, this subgroup of Oatrim was not known as BetaTrim™. In their paper, the investigators refer to the test products as Oatrim-1 and Oatrim-10. The investigators also interchangeably refer to Oatrim-1 &-10 as "oat extracts" or "Oatrim" in their scientific publications and other related materials. However, note that in this petition we make a distinction between purified "oat extracts and gums" versus Oatrim. We reserve the use of the term "oat extracts and oat gums" to refer to the more highly concentrated processed β-glucan soluble fibers with β-glucan concentrations above 60%. Our use of the term "oat extract" is synonymous with the term "oat gum".

Therefore, the results of this study demonstrate that the oat β-glucan from Oatrim-1 and Oatrim–10, consumed at 1.6-8.4 g per day were both effective in lowering total- and LDL-cholesterol.

Although the term "Oatrim" has not been used in other human studies, there are two studies (Pick et al, 1996; Torronen et al, 1992) that have used processed oat bran concentrates, which by their description and through personal communication would be considered Oatrim products. Pick et al (1996) reported on the hypocholesterolemic properties of a high-β-glucan oat bran concentrate with a 22.8% β-glucan concentration (dose: 40 g of concentrate; 9.0 g β-glucan), consumed every day for 12 weeks by subjects with normal blood cholesterol levels, consuming a low fat diet. This high-β-glucan oat bran concentrate reduced total cholesterol by 14% ($p < 0.01$) and LDL-cholesterol by 23% ($p < 0.01$) compared to white bread placebo. Dietary fat intake and body weight remained constant throughout the study. This study supports the cholesterol-lowering efficacy of processed β-glucan soluble fibers at a concentration of 23% [i.e. Oatrim (BetaTrim™-20)].

On the other hand, Torronen et al (1992) observed no significant effects between the oat and control intervention periods when processed oat bran concentrate containing 15% β-glucan (dose: 11.2 g β-glucan per day) was evaluated in hypercholesterolemics for 8 weeks. The authors concluded that the wet milling and sieving in cold-water suspension method used in concentrating and processing oat bran, made the β-glucan ineffective. The investigators also reported that in an animal study conducted by them using a similar preparation of oat bran concentrate, they observed that the weak effect of the β-glucan was attributed to its poor solubility, enzymatic hydrolysis after ingestion, and low viscosity in the intestine. This study demonstrates the importance and critical impact of the type of processing on cholesterol-lowering efficacy and illustrates the need to evaluate each processed β-glucan soluble fiber for its ability to retain such properties.

Two additional human studies have evaluated processed β-glucan soluble fibers (Braaten et al, 1994a; Beer et al, 1995), but in the form of oat extracts or oat gums. It is unlikely that

these products would be considered Oatrim ingredients since they are highly concentrated and purified sources of β-glucan soluble fiber. Nevertheless, these two studies are reviewed because they used processed and purified oat β-glucan soluble fiber ingredients and provide further evidence for the cholesterol lowering efficacy of processed soluble oat fibers. Braaten et al (1994a) evaluated the cholesterol-lowering effects of an instant oat gum comprised of 80% β-glucan consumed daily for four weeks by hypercholesterolemic subjects eating their usual diets (dose: 7.2 g of oat gum; 5.8 g β-glucan). Compared to baseline, oat gum consumption reduced total cholesterol by 9.2% ($p< 0.0001$) and LDL-cholesterol by 10% ($p<0.001$). There were no significant changes in nutrient intake during the oat and placebo phases, and body weight also remained stable.

Beer et al (1995) tested an oat gum comprising 62.2% β-glucan as an instant whip (dose: 9 g β-glucan per day) in normocholesterolemic subjects for two weeks and observed no significant differences in serum cholesterol between the oat and control periods. The authors suggest that the low viscosity of the oat gum in the gut and the low baseline serum cholesterol values of the subjects may have contributed to the lack of an effect. However, this study would not have met FDA's criteria for evaluating studies because the treatment phase only lasted two weeks. FDA and experts in the field have stated that the intervention period needs to be long enough (three weeks or greater) to ensure that blood lipids have stabilized.

All of these studies reviewed with the exception of Beer et al, 1995 met FDA's criteria for selection of human studies—i.e. had presented data and had adequate descriptions of study design and methods; were available in English; had information on soluble dietary fiber (β-glucan); included measurement of blood total cholesterol and other blood lipids related to CHD; were conducted in persons who represent the general U.S. population (i.e. adults with blood total cholesterol less than 300 mg/dL); and had treatment phases longer than three weeks. Three of the studies (Braaten et al, 1994a; Pick et al, 1996; Behall et al, 1997) were randomized crossover trials; the fourth was a randomized, placebo controlled intervention (Torronen et al, 1992). Two studies (Braaten et al, 1994a; Torronen et al, 1992) evaluated hypercholesterolemic subjects consuming "typical" or "usual" diets, one study evaluated

hypercholesterolemic subjects consuming a low fat diet (Behall et al, 1997), and one study evaluated normocholesterolemic subjects consuming a low fat diet (Pick et al, 1996). Overall, two human studies demonstrate the cholesterol-lowering potential of Oatrim, including Oatrim (BetaTrim™) (Behall et al, 1997; Pick et al, 1996). One additional human study, which utilized oat gum (i.e. purified, concentrated source of oat β-glucan soluble fibers), is supportive of the cholesterol-lowering potential of processed β-glucan soluble fibers of which Oatrims are a part (Braaten et al, 1994a). The concentrations of β-glucan soluble fiber sources in the Oatrim studies ranged from 1.6% to 23%. The 4-25% β-glucan range of Oatrim (BetaTrim™), which is the focus of this petition, falls within this tested range, whereas the β-glucan concentration of the oat gums or oat extracts (i.e. 60% to 80%) fall outside of this range.

2. Summary of Human Evidence

Behall et al, (1997) demonstrated effective serum cholesterol reduction with Oatrim (BetaTrim™), The Quaker-Rhodia Partnership brand of Oatrim and ConAgra's Oatrim, in the form of Oatrim-10 (10.2% or 5.1-7.6 g of β-glucan soluble fiber from Oatrim) and Oatrim-1 (1.6% at 0.8-1.2 g of β-glucan soluble fiber from Oatrim). The study by Pick et al (1996) further demonstrates the cholesterol-lowering ability of a processed oat bran concentrate source (also an Oatrim) with 22.8% of processed β-glucan soluble fiber content. At adequate levels of intake, these two studies confirm the cholesterol-lowering efficacy of low (i.e. 1.6%), medium (i.e. 10.2%) to high (i.e. 22.8%) concentrations of processed β-glucan soluble fiber in Oatrim (BetaTrim™) and other Oatrim (i.e. oat bran concentrate) products. Although extracted oat gums are not generally considered Oatrim, the results of the Braaten et al (1994b) study is additional support for the cholesterol-lowering potential of extracted and processed oat β-glucan soluble fibers. The data clearly demonstrate that certain processed oat β-glucan fibers remain efficacious when incorporated into food products as sources of soluble fiber (Behall et al, 1997; Pick et al, 1996; Braaten et al, 1994a). The lack of cholesterol-lowering efficacy of the processed oat bran concentrate used in the Torronen et al (1992) study was attributed to the type of processing method used. Therefore, it is important

that appropriate processing and extraction procedures be used to ensure the cholesterol-lowering efficacy of processed β-glucan soluble fiber sources.

Overall, the human clinical data show that consumption of approximately 1.6–9 g of β-glucan per day from Oatrim (BetaTrim™) and other Oatrim products significantly reduce total- and LDL- cholesterol. Therefore we conclude an effective dose of 3 g of β-glucan per day as previously established in the Soluble Fiber Health Claim Final Rule (21 CFR 101.81) is also appropriate as the effective dose of β-glucan from Oatrim (BetaTrim™). Thus, these data demonstrate that Oatrim (BetaTrim™) containing foods can reduce total- and LDL-cholesterol and CHD risk.

C. ANIMAL DATA

1. Applicability of Animal Studies (Appendix 7)

Animal studies are useful in confirming the results of human studies and demonstrating mechanisms by which a substance exerts its effect in the body. In the case of soluble fiber and serum cholesterol reduction, numerous animal studies have demonstrated that oat β-glucan soluble fiber (Chen et al, 1981; Oda et al, 1994; Oda et al, 1993; Welch et al, 1988; Malkki et al, 1995; Ranhotra et al, 1990; Inglett and Newman, 1994b; Yokoyama et al, 1998) and psyllium soluble fiber (Trautwein et al, 1999; Arjmandi et al, 1997; Fernandez et al, 1995; Turley and Dietschy, 1995) lower both serum and liver cholesterol, affirming the work done in humans. When FDA was considering expanding the oat health claim to include whole oat flour, one human study (Reynolds, unpublished study, 1996) and several animal studies (Gallaher et al, 1999*: this study was unpublished when reviewed by FDA in 1996*; Shinnick et al, 1993; Shinnick et al, 1988; Ney et al, 1988) were used as evidence in substantiating a positive effect of ready-to-eat cereals made with whole oat flour on serum cholesterol and reduced risk of CHD.

Human studies are expensive to conduct. Hence, it has been suggested that for the routine testing of the cholesterol-lowering capacity of food products/ingredients, a marker of cholesterol-lowering potential would be of great use (Gallaher et al, 1999). The results of

several animal studies suggest that intestinal contents supernatant viscosity could be such a marker.

Using cholesterol-fed hamsters, Gallaher et al (1993a) showed that increased viscosity of the intestinal contents is associated with reductions in both plasma and liver cholesterol. In a subsequent study, Gallaher et al (1993b) demonstrated that this relationship was highly predictable, since the log of intestinal contents viscosity is inversely related to plasma cholesterol. Carr et al (1996) found that as intestinal viscosity increases, excretion of neutral sterols increases and cholesterol absorption decreases. Interference with cholesterol absorption has been suggested as a primary mechanism through which increased intestinal viscosity lowers plasma cholesterol. The shape of the curve between log intestinal contents viscosity and daily sterol excretion is the inverse of the log intestinal contents viscosity and plasma cholesterol curve. The relationship between increased intestinal contents viscosity, reduced liver cholesterol concentrations, and reduced cholesterol absorption have been confirmed in the hamster and rat models, and with the following viscous fibers: guar gum, hyroxypropyl methylcellulose (HPMC), and oat β-glucan fibers (Carr et al, 1996; Gallaher et al, 1993a; Gallaher et al, 1993b; Osterberg et al, 1993).

2. Gut Viscosity[5] Animal Studies: An Acceptable Model for Inclusion of Oat Flour and Oatrim (BetaTrim™)

FDA has acknowledged in the final rule (62 FR 3584) that the viscosity of intestinal contents is a critical factor in determining the ability of soluble fibers to reduce the risk of CHD (Wood, 1993; Gallaher et al, 1993a; Carr et al, 1996). The agency noted that viscosity is affected by food processing procedures in ways that are unpredictable [62 FR 3586, January 23, 1997: Section II(3)]. Therefore FDA stated that crucial to the question of whether oat flour can provide the same benefits as rolled oats is evidence that demonstrates that β-glucan soluble fiber from whole oat flour retains the same level of viscosity in the digestive tract as that from rolled oats [62 FR 3586, January 23, 1997: Section II(3)]. Animal studies cited by Gallaher in comments to FDA (comment C-1412/see Appendix 8) adequately demonstrated

[5]Refers to intestinal contents supernatant viscosity.

bioequivalence relative to these physical characteristics between rolled oats and whole oat flour.

Gallaher et al (1999; and comment C-1412) evaluated the intestinal contents supernatant viscosity of oatmeal, oat bran, and Cheerios, an oat flour based ready-to-eat cereal in cholesterol-fed rats using the same protocol previously used to measure the effect of hyroxypropyl methylcellulose (HPMC) in cholesterol-fed hamsters (Gallaher et al, 1993b). The viscosity achieved by all the cereals (oatmeal, oat bran, Cheerios) tested, if extrapolated to the hamster study, would have produced significant reduction in plasma cholesterol. In his comments (comment C-1412), Gallaher stated that:

> "since Cheerios, oatmeal, and oat bran all have been demonstrated to reduce plasma cholesterol in humans, I believe our viscosity results obtained in rats (*see Figure 1 in this petition*) are applicable to the human situation. That is, I suggest that our results indicate that consumption of any of these cereals by humans, at their recommended serving size, would produce intestinal viscosity sufficient to reduce cholesterol absorption and thereby lower plasma cholesterol. Further, I believe viscosity values obtained in animals may be useful as a predictor of the cholesterol-lowering of other foods containing certain soluble fibers potential."

Recently, Gallaher[6] and coworkers conducted three additional studies: In the first study (Freiburger and Gallaher, 2000), intestinal contents supernatant viscosity was measured after meal-feeding rats the following fiber sources: oatmeal (i.e. rolled oats), cellulose (control), or three concentrations of Oatrim (BetaTrim™) namely, 4, 12, and 20% β-glucan content[7]. These Oatrim (BetaTrim™) ingredients were processed by the enzymatic method (Appendix 1A). Results from the first study indicated that the intestinal supernatant viscosity

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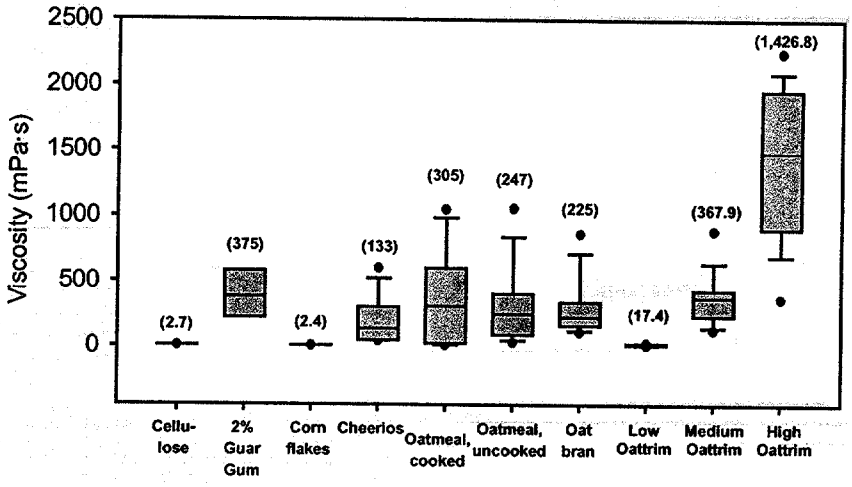
[6]See letter from Dr. Daniel Gallaher, University of Minnesota (Appendix 9) that supports the accurate representation of his unpublished animal data by the petitioners in this petition. The letter also supports the cholesterol-lowering efficacy of Oatrim (BetaTrim™).

[7] The sources of oat-β-glucan used were The Quaker-Rhodia Partnership's commercially available Oatrim (BetaTrim™) -5 (due to processing variability contained 4% oat-β-glucan) and Oatrim (BetaTrim™) –20 (contained 20% oat-β-glucan). The Oatrim (BetaTrim™) –12 used in this study was made by mixing Oatrim (BetaTrim™) –5 &-20 to give a mid-level Oatrim (BetaTrim™)-12 (i.e. 12% oat-β-glucan).

Figure 1[£,§]

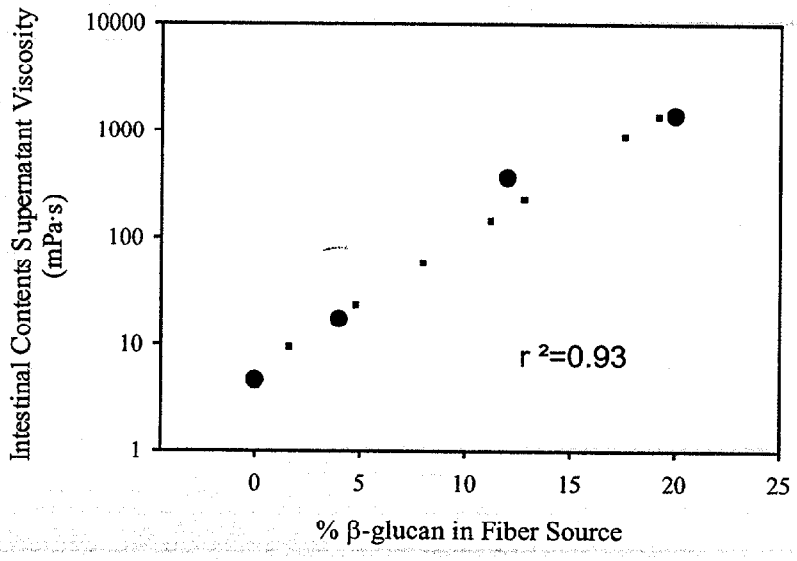
Intestinal Contents Supernatant Viscosity
of Rats Meal-Fed Fibers or Different Cereals



[£]Reproduced in part from Gallaher, 1999 (with permission)
[§]The low, medium and high Oatrims are Oatrim (BetaTrim™) -4%, -12%, and -20%.

Figure 2

Correlation Between Dietary β-Glucan Concentration
and Intestinal Contents Supernatant Viscosity
in Rats Meal-Fed Oattrim (BetaTrim) of Different Viscosities



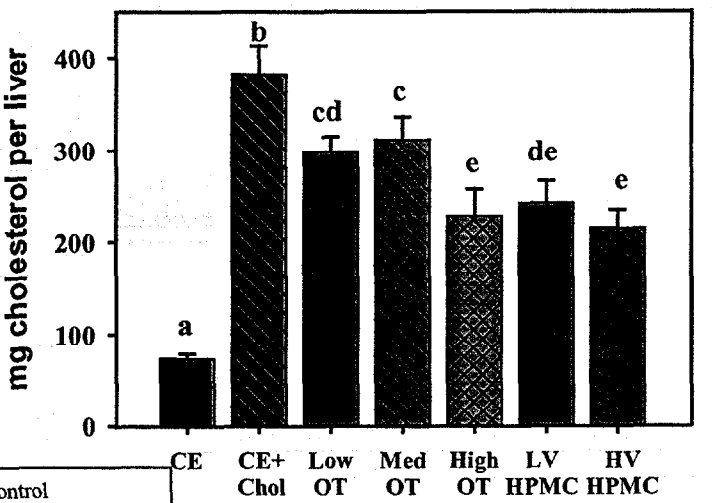
progressively increases from the low to high concentrations of Oatrim (BetaTrim™). The 12% and 20% β-glucan Oatrim (BetaTrim™) produced intestinal viscosities similar to and significantly greater than oatmeal and oat bran (see Figure 1). A strong correlation was observed between the dietary β-glucan concentration and intestinal contents supernatant viscosity (Figure 2). The protocol of this study was identical to the one utilized in evaluating Cheerios (Gallaher, 1999; comment C-1412 submitted and approved for the soluble fiber & CHD health claim).

In addition to the intestinal viscosity assessment in meal-fed animals, a second animal study, a chronic feeding study was also conducted with the low (4%), medium (12 %), and high (20 %) β-glucan containing Oatrim (BetaTrim™) (Freiburger and Gallaher, 2000; Freiburger and Gallaher, 2001). High viscosity hydroxypropyl methylcellulose (HV-HPMC), low viscosity LV-HPMC, and a cellulose control (with and without cholesterol) were also tested. In this study the animals were chronically fed the test products for a month. Results from both the meal-fed study and the chronic feeding trial indicate that intestinal contents supernatant viscosity increases in a linear manner as the β-glucan content in the meal or diet increases. All five fiber sources lowered liver cholesterol compared to the cellulose controls (Figure 3). There was a dose response effect among the Oatrim (BetaTrim™) products, such that the highest reduction in total liver cholesterol was observed with the greatest concentration of β-glucan (i.e., 20% β-glucan/ Oatrim (BetaTrim™)-20. As observed in previous work (Gallaher et al, 1993b), a significant inverse correlation between total liver cholesterol and log intestinal contents supernatant viscosity was also observed (data not shown). It was further noted that the absolute intestinal viscosity values obtained after chronic feeding were lower than the absolute viscosities observed in the single meal-fed studies (Freiburger and Gallaher, 2000/study 1 and Gallaher et al, 1999/the Cheerios study).

During chronic feeding some physiological adaptation takes place, however, despite this adaptation significant cholesterol lowering was observed with all three Oatrim (BetaTrim™). This study also attempted to identify the mechanisms through which Oatrim (BetaTrim™) lower cholesterol. Unexpectedly, the total liver cholesterol reduction that was observed with

Figure 3

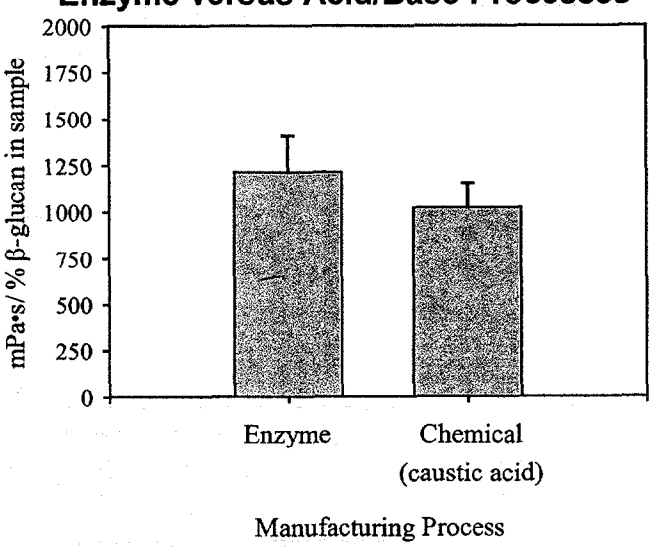
Total Liver Cholesterol in Rats Fed Oatrim (OT) or Hydroxypropyl Methylcellulose (HPMC)



CE: Cellulose control
CE+Chol: Control +cholesterol
Low OT: 4% Oatrim
Med OT: 12% Oatrim
High OT: 20% Oatrim
LV HPMC: low viscosity hydroxypropyl methylcellulose
HV HPMC: high viscosity hydroxypropyl methylcellulose

Figure 4

Oatrim (BetaTrim™)-20 Contents Supernatant Viscosity Enzyme versus Acid/Base Processes



There is no statistically significant difference between the groups (p=0.43)

Oatrim (BetaTrim™) at all levels of β-glucan tested, appeared to have been influenced to a greater degree by increased fecal bile acid excretion than by reduced cholesterol absorption. The data from this study also demonstrated that regardless of the level of β-glucan, fermentation was less important than viscosity.

The third study (Gallaher et al, unpublished) was also a meal-feeding study, using the same protocol from study 1 (Freiburger and Gallaher, 2000). The aim of this study was to compare intestinal contents supernatant viscosity, using 20% β-glucan or High Oatrim (BetaTrim™) from two different processing methods, i.e. an enzymatic method and an acid/base method (Appendices 1A & 1B). The intestinal contents supernatant viscosity per unit β-glucan results (Figure 4) indicate no statistically significant difference between the two 20% β-glucan Oatrim (BetaTrim™) processed from either acid/base and enzymatic processes. Therefore, the results of the third study demonstrates that Oatrim (BetaTrim™) from both manufacturing methods (i.e. enzymatic and acid/base methods) are equally effective at increasing intestinal contents supernatant viscosity.

When taken together, the results from the three Gallaher studies (Freiburger and Gallaher, 2000; Freiburger and Gallaher, 2001; and Gallaher's unpublished 3rd study) indicate that Oatrim (BetaTrim™) -4, -12, and –20 are effective in reducing cholesterol levels. The enzymatic and acid/base methods used to process these Oatrim (BetaTrim™) products from whole oat flour and/or oat bran do not diminish their physiological effectiveness in increasing intestinal contents supernatant viscosity and lowering cholesterol. The total liver cholesterol reduction did not follow a linear relationship with increasing dietary concentrations of Oatrim (BetaTrim™), however, the greatest cholesterol reduction was observed with the highest dietary level of Oatrim (BetaTrim™) and significant cholesterol reduction occurred even at very low viscosity [i.e. Oatrim (BetaTrim™)-4]. The effectiveness of oat β-glucans is proportional to the logarithm of the viscosity. A significant proportion of the cholesterol lowering effectiveness is attributable to viscosity, which can occur at very low viscosity. Oatrim (BetaTrim™)-4% to 20% lowered total cholesterol to almost the same extent.

The precise mechanism by which oat soluble fiber β-glucan lowers cholesterol is not completely understood, however the cholesterol reduction observed was partly explained by increased fecal bile acid excretion. These data, as well as previously published data on rolled oats and oat bran, suggest that the cholesterol lowering ability of oats and processed oat soluble fibers may be due to multiple factors which include (but are not limited to), the concentration of β-glucan soluble fiber, increased intestinal contents supernatant viscosity, increased bile acid excretion and reduced cholesterol absorption.

3. Other Animal Studies Evaluating Oatrim or Concentrated Oat β-glucan

Other animal studies that have evaluated the cholesterol-lowering effects of Oatrim (including oat bran concentrates) and oat gums are summarized in Appendix 7. The Oatrim and oat bran concentrates used in these studies had β-glucan concentrations ranging from 1.5% to 14% (Inglett and Newman 1994; Inglett et al, 1994; Yokoyama et al, 1998), whereas oat gum studies used β-glucan concentrations ranging from 51.1% to 66% (Chen et al, 1981; Oda et al, 1994; Oda et al, 1993; Welch et al, 1988). In all instances, total plasma cholesterol was significantly lowered, as was LDL-cholesterol and liver cholesterol, when it was measured.

Inglett (the chemist who first developed Oatrim) and colleagues evaluated Oatrim in three studies (Inglett and Newman, 1994; Inglett et al, 1994; Yokoyama et al, 1998). In the first study, Inglett and Newman (1994) used Oatrim-10 (a 10% β-glucan source) at 26.4% of the chick diet for 10 days and found total plasma cholesterol was reduced by 18% and LDL-cholesterol by 48% compared to controls. The chicks fed Oatrim also gained significantly less weight than the controls (which may have influenced plasma lipids in part). Inglett and coworkers (1994) conducted a follow-up study with Oatrim-10 (a 8.6% β-glucan source) in a larger sample of chicks and found the cholesterol lowering results confirmed the earlier study. In comparison to controls, total plasma cholesterol was reduced by 40% and LDL-cholesterol by 61%. Yokoyama et al (1998) fed hamsters diets containing 39.6% Oatrim-10 (a 10.6% β-glucan source) and 67.3% Oatrim-5 (a 6.4% β-glucan source) for 21 days and found a 36% reduction in total cholesterol and 42% reduction in LDL-cholesterol for Oatrim-10 and a 32% reduction of total cholesterol and 67% reduction of LDL-cholesterol for

Oatrim-5. The greater LDL-cholesterol-lowering effect of Oatrim-5 compared to Oatrim-10 differs from the results of other studies that observed more significant plasma cholesterol reductions with the higher β-glucan containing Oatrims. An oat hydrolyzate fed at 40.1% of the diet was also effective in lowering total plasma cholesterol and LDL-cholesterol in these animals, despite the fact that the oat hydrolyzate contained no β-glucan (the authors speculate that components other than β-glucan were likely responsible for this effect). In the same study, a diet with 14.9% enriched oat flour (a 29.1% β-glucan source) was also tested, but did not produce significant cholesterol lowering. The molecular weight of β-glucan from Oatrim-10 and Oatrim-5 were 66% to 58% lower respectively, than the molecular weight of β- glucan from the enriched oat flour. Furthermore, the ratio of β-glucan molecular weight to volume calculated from radii indicated the ratio for enriched oat flour was ten times larger than the ratio for both Oatrims. It was concluded that these factors might have influenced polydispersity and viscosity in the gut.

Malkki et al (1995) tested an oat bran concentrate at three different levels of β-glucan (1.5%, 3.0%, and 4.5%) and found all levels of β-glucan lowered plasma cholesterol, but were unable to demonstrate a dose response relationship. However, the authors stated that observations from their work showed the superiority of the hypocholesterolemic effect of the processed oat bran concentrate over untreated oat bran at similar levels of β-glucan. Ranhotra et al (1990) observed that a processed oat bran concentrate (14% soluble fiber β-glucan) had a more pronounced serum cholesterol-lowering effect than oat bran (6% soluble fiber β-glucan) fed at the same dietary level (50%) in both hypercholesterolemic and normocholesterolemic rats. Processing of oat bran into an oat bran concentrate significantly increased the soluble fiber content, so that compared to oat bran, lower amounts of oat bran concentrate were needed to obtain similar results in hypercholesterolemic animals. When oat bran concentrate was fed at 20.7% of the diet, a level that would have the same level of soluble fiber as oat bran fed at 50% of the diet, the cholesterol-lowering effects of the two products were similar in hypercholesterolemic rats, but more pronounced in normocholesterolemic rats. The authors state the significant cholesterol-lowering of the processed oat bran concentrate at both the high (50%) and low (20.7%) levels in the diet

among normocholesterolemics may suggest a "uniqueness" of the soluble fiber in oat bran concentrate which made it more effective than the soluble fiber in regular untreated oat bran. However the authors also suggest caution in this interpretation because the caloric density of the processed oat bran concentrate diets was low compared to the other diets, as this may have been a contributing factor in the hypocholesterolemic effect of processed oat bran concentrate.

Welch et al (1988) and Oda et al (1994; 1993) evaluated oat gums fed between 1.9% to 3.4% of the diet. The β-glucan concentrations of the oat gums ranged from 51.1% to 65%. These studies observed significant reductions in serum and liver cholesterol levels compared to controls. Serum and liver triglycerides were also reduced in the study by Oda et al (1994).

4. Summary of Animal Evidence

FDA has acknowledged that the viscosity of intestinal contents is a critical factor in determining the ability of soluble fibers to reduce CHD risk. Gallaher and coworkers have demonstrated that intestinal contents supernatant viscosity could be a useful marker for the cholesterol-lowering capacity of foods. This method was used in part to demonstrate the bioequivalence of whole oat flour to oatmeal (i.e. rolled oats) and oat bran.

Three recent studies were conducted by Gallaher using Oatrim (BetaTrim™) –4%, 12%, and 20%. The first single meal-fed study noted that intestinal supernatant viscosity increased from the low to high concentrations of Oatrim (BetaTrim™) and that the intestinal viscosity of Oatrim (BetaTrim™) was similar to and greater than oatmeal (i.e. rolled oats) and oat bran. The second chronic feeding study, a rat cholesterol feeding study demonstrated a dose response effect on liver cholesterol, with the highest reduction in liver cholesterol observed with 20% β-glucan Oatrim (BetaTrim™). A significant inverse correlation between total liver cholesterol and log intestinal contents supernatant viscosity was also observed and significant cholesterol reduction occurred at very low viscosity. In this animal study, it appeared that increased fecal bile acid excretion appeared to be an important contributing factor by which Oatrim (BetaTrim™) lowered rat liver cholesterol. The third study, another rat cholesterol feeding study, compared the intestinal supernatant viscosity of 20% β-glucan

Oatrim (BetaTrim™) from two different processing methods, i.e. an enzymatic method versus an acid/base method. There were no statistically significant differences in the results from both methods.

Several other researchers have conducted animal feeding studies with other Oatrim products (also referred to as, oat bran concentrates). The β-glucan concentration in these products ranged from 1.5% to 14%. In all the studies total plasma cholesterol was significantly lowered, as was LDL-cholesterol, and liver cholesterol[8]. Animal studies with oat gum (β-glucan concentrations from 59.5% to 65%) also demonstrated significant serum and liver cholesterol reductions.

Overall, the results of several *in vivo* studies of Oatrim (BetaTrim™) and other Oatrim sources have demonstrated the effectiveness of oat-β-glucan from these sources in lowering total- and LDL- cholesterol. Further, the results of intestinal supernatant viscosity studies on Oatrim (BetaTrim™) provide evidence that Oatrim (BetaTrim™) retains its viscous properties and has the ability to effectively lower cholesterol. These data also demonstrate the efficacy of Oatrim (BetaTrim™) manufactured from two different processing methods outlined in this petition.

D. BIOEQUIVALENCE OF OATRIM (BETATRIM™)

Overall, the scientific data demonstrate the bioequivalence of β-glucan soluble fiber in Oatrim (BetaTrim™) to β-glucan soluble fiber in rolled oats, oat bran, and whole oat flour.

[8]Even though the mechanisms are not completely understood and there is no clear agreement on which mechanisms and/or factors (i.e., reduced cholesterol absorption, increased bile acid excretion, beta-glucan concentration, or molecular weight) specifically cause oats and/or the beta-glucan in oats to have beneficial cholesterol-lowering properties, scientists and governmental bodies do agree that the beta-glucan in oats is the primary factor responsible for lowering serum total-and LDL-cholesterol.

In summary:

- It has been previously confirmed that β-glucan soluble fiber is the primary component responsible for the cholesterol-lowering effect of rolled oats, oat bran and whole oat flour. Oatrim (BetaTrim™) is a concentrated source of β-glucan, and therefore appropriate to be considered for inclusion in the health claim authorizing β-glucan soluble fiber from oats.
- Oatrim (BetaTrim™) is somewhat different in its physical composition compared to rolled oats, but is derived from oat bran or whole oat flour, the same starting materials as whole rolled oats, oat bran, and whole oat flour in the original petition.
- Using human study protocols similar to those used in the evaluation of rolled oats and oat bran, it has been shown that Oatrim (BetaTrim™) lowers total-and LDL-cholesterol similar to rolled oats and oat bran.
- Using animal study protocols similar to those considered and approved by FDA in the evaluation of whole oat flour, it has been demonstrated that Oatrim (BetaTrim™) retains sufficient levels of viscosity in the digestive tract to lower cholesterol. The viscosity of Oatrim (BetaTrim™) is similar to and greater than rolled oats, oat bran and whole oat flour products, therefore, can provide the same benefits as rolled oats. An animal feeding trial of different β-glucan concentrations (4%, 12% and 20%) of Oatrim (BetaTrim™) also demonstrated a significant inverse correlation between total liver cholesterol and log viscosity.

E. OTHER POTENTIAL HEALTH EFFECTS

In addition to the beneficial effects on lipoproteins, dietary fiber and oat soluble fibers have been shown to have a positive influence on blood glucose control, satiety and obesity, and blood pressure, some of which are also independent risk factors for coronary heart disease.

1. Beneficial Effects on Glucose Tolerance and Insulin Resistance

Recent research has shown various grains, grain based products, and grain extracts such as processed oat β-glucan soluble fibers to be effective in improving glucose tolerance and reducing insulin resistance. In the original Quaker oat health claim petition, research

suggesting that oat consumption may improve blood glucose and insulin regulation was summarized. The petition noted that oat β-glucan soluble fiber extracted from oat bran, and oat bran itself, reduce postprandial glucose and insulin levels in a pattern similar to the action of guar gum in both healthy and diabetic subjects (Wood et al, 1990; Braaten et al, 1991; Braaten et al, 1994b). All three studies, utilized the same oat gum product, comprising 80% β-glucan. The viscosity of oat β-glucan soluble fiber has been implicated as the factor responsible for the favorable effect of oats on blood glucose (Wood et al, 1990).

Additional studies since the Quaker oat health claim petition lends further support that oat β-glucan soluble fiber may help improve glycemic control. Some of the studies utilized Oatrim or processed oat bran concentrate (Hallfrisch et al, 1995; Pick et al, 1996; Tappy et al, 1996), whereas others used oat gums (Wood et al, 1994; Wood et al, 2000).

Hallfrisch et al (1995) conducted the first long-term controlled human study of oat β-glucan on glucose tolerance in a group of moderately hypercholesterolemic subjects. These researchers measured the effect of 1.6% (1.6 – 2.0 g per day) or 10.2% (5.9 – 8.4 g per day) Oatrims (Oatrim-1 & -10) in a 11-week crossover study of two 5-week periods. The Oatrims substituted 10% of energy in the diet by replacing some of the carbohydrate and fat in foods that included baked goods, juices, desserts, meat loaf, and soup. Glucose tolerance tests at the end of each 5-week period indicated significant declines in glucose, insulin, and glucagon with both Oatrims. Concentrations of insulin, and glucagon were lower after the consumption of Oatrim-10 than the Oatrim-1. This trend was not evident for glucose concentrations. Subjects experienced some weight loss in this study, but the researchers indicated the weight loss was small and did not correlate with glucose and insulin changes.

Another long-term human feeding study of oat β-glucan and glycemic control was conducted in type 2 diabetic subjects (Pick et al, 1996). The effect of 9 g per day of β-glucan in 40 g of oat bran concentrate (from a 22.8% β-glucan source) incorporated into bread products was evaluated in a 24-week crossover study of two 12-week periods. Blood glucose and insulin profiles were measured at baseline and at the end of each 12-week period. Results indicated a significant improvement in blood glucose control. The increase in postprandial blood

glucose area under the curve was less in the oat bran concentrate period than in the white bread (placebo) period. Similarly, the total insulin response and peak insulin values were lower in the oat bran concentrate period than in the white bread period.

Tappy et al (1996) evaluated plasma glucose and insulin responses in subjects with type 2 diabetes with increasing doses (4, 6, and 8.4 g) of β-glucan present in an extruded breakfast cereal containing oat bran concentrate. All three doses of β-glucan attenuated plasma glucose and insulin responses after the consumption of a carbohydrate load. The 4 g dose lowered glycemia by 33% and the 6 g and 8.4 g doses lowered glycemia by 60%. The authors concluded that significant glycemic benefit could be derived from cereal containing 10% or 6 g β-glucan.

Wood et al (1994) found that increasing the dose of oat gum (containing 80% β-glucan) produced a maximum attenuation (40%) in peak glucose with 7.2 g of oat gum, with little additional effect with increased quantities of β-glucan. Reducing viscosity of the oat gum by acid hydrolysis methods reduced or eliminated the ability to lower postprandial glucose and insulin levels. Addition of maltodextrin to the oat gum mixture to improve dispersity (and palatability) in a drink did not modify the glycemic ability of the oat gum. There was a highly significant linear relationship between log [viscosity] of the mixture consumed and the glucose and insulin responses. The data demonstrated that 79-96% of the changes in plasma glucose and insulin was attributable to viscosity. Despite a threshold level for a physiologically effective response, the regression suggested that even at relatively low doses (1.8 g oat gum) and viscosities, there was attenuation of peak plasma (12-13%) glucose following an oral glucose load. Recently, Wood et al (2000) reanalyzed the data in this study to evaluate the role of concentration and molecular weight of oat β-glucan in determining the effect of viscosity on plasma glucose and insulin response. A significant relationship between change in peak blood glucose and a combination of logarithm of the concentration and logarithm of molecular weight was found.

These studies demonstrate that a diet high in total and soluble fiber can be useful for diabetics in the management of blood glucose and insulin responses. In their review of

soluble fiber in the metabolic control of diabetes, Wursch and Pi-Sunyer (1997) report that β-glucan may be the most effective soluble fiber in normalizing blood glucose and insulin levels. However, the type of processing that oat products are subjected to can impact the outcome. Heaton et al (1988) found that whole grain oats and oat flour evoked similar glucose and insulin responses. However, Liljeberg et al (1992) found that boiling oat kernels before incorporation into a coarse bread elicited a glycemic index similar to white bread. Insulin responses on the other hand were significantly lower for the oat coarse bread than the white bread. Granfeldt et al (1995) also reported that rolled oats and oat porridge produced glycemic and insulinemic indices similar to white wheat bread. Steaming and rolling oat grains result in the disruption of tissue, increasing the accessibility of the starch to digestion, and subsequently increasing blood glucose and insulin responses. Recently Granfeldt et al (2000) demonstrated that the thickness of rolled oats also influences the glycemic index. These researchers found that thin flakes elicit high glucose and insulin responses, whereas thick flakes significantly lower glycemic responses.

Overall, all the studies on oat β-glucan concentrated sources, such as Oatrim or oat bran concentrate (Hallfrisch et al, 1995; Pick et al, 1996; Tappy et al, 1998b) and oat gum (Wood et al, 1990; Wood et al, 1994; Braaten 1991; 1994b), demonstrate that based on the type of processing used, processed oat β-glucan maintained or enhanced the glycemic properties of the oat β-glucan product.

2. Beneficial Blood Pressure Effects

Hypertension is one of the most prevalent cardiovascular disorders in the United States (U.S.) and affects over 50 million Americans (Burt et al, 1995; Sutherland et al, 1994). A population wide, modest reduction of 5 mm Hg in diastolic blood pressure (DBP) would predictively prevent, approximately 100,000 strokes per year in the U.S. (Pins et al, 1999).

Increased dietary fiber intakes have been associated with lower levels of systolic blood pressure (SBP) as well as DBP (Ascherio et al, 1996; Witteman et al, 1989; Joffres et al, 1987) in epidemiological studies. Additionally, studies comparing vegans with lacto-ovo vegetarians and non-vegetarians also support a relationship between dietary fiber and blood

pressure (BP) (Armstrong et al, 1987). In the Caerphilly Heart Study of South Wales, low daily cereal fiber intake was significantly associated with elevated BP after adjusting for age, body mass index, ischemic heart disease, and heart rate (Lichtenstein et al, 1986; Elliott et al, 1987). In an observational study among Chinese men and women, He et al, (1995) investigated the relationship between dietary fiber from specific cereal sources (oats and buckwheat) and blood pressure. Before and after adjusting for confounders, using multivariate regression analysis, these results showed oat intake was significantly and inversely associated with both SBP and DBP. Furthermore, this association was attributed to the soluble fiber intake and not to total dietary fiber intake.

Most recently, Keenan and colleagues (Keenan et al, 1998; Pins et al, 1999) conducted two clinical trials utilizing a mostly soluble fiber intervention from oat based cereals compared to a mostly insoluble wheat based cereal intervention. In the first trial among untreated hypertensives, the oat-based intervention group experienced a significant reduction in SBP (7.5 mm Hg) and DBP (5.5 mm Hg) after a 6-week intervention period compared to observed reduction in the wheat-based group. The second trial was conducted for 12 weeks among treated hypertensives using the same type of oat or wheat-based intervention as the first trial. After 12 weeks, a significant percent of the participants in the oat-based intervention group eliminated their need for medication; however, this was not observed in the wheat-based control group.

These data suggest that dietary fiber, especially soluble viscous fibers such as oat β-glucan soluble fiber, including the β-glucan from Oatrim (BetaTrim™) may have an important positive influence on blood pressure. Although the exact mechanism relating fiber and hypertension is still not clear, it is possible that it may be mediated through its influence on insulin resistance and endothelial function (Katakam et al, 1998; Pins et al, 1999).

3. No Significant Adverse Effects

Studies to date do not provide evidence of any significant adverse effects related to oat fiber intake and gastrointestinal disturbances, choking or vitamin-mineral mal-absorption. Additionally, the estimations using nationally representative data, on increased total and

soluble dietary fiber intakes from greater oat β-glucan intakes with Oatrim (BetaTrim™) containing foods, do not indicate that fiber intakes will rise to levels that warrant the need for concern[9].

a) No Reported Significant Adverse Gastrointestinal Disturbances or Choking

Oat β-glucan products, such as Oatrim, including Oatrim (BetaTrim™), processed β-glucan concentrates, oat-gums and powders, as ingredients and/or as sources of soluble fiber, have been incorporated into products and have been well accepted, in several clinical studies at varying levels of β-glucan, in the form of muffins, cereals, beverages and breads. Overall, apart from some mild and short-lived gastrointestinal side effects such as flatulence and abdominal discomfort, no major gastrointestinal or esophageal obstructions have been reported (Beer et al, 1995; Behall et al,1998; Behall et al, 1997). Gastrointestinal side effects have usually been reported by individuals who shifted abruptly to a high fiber intake from what was typically a low fiber diet. These effects may be reduced by gradually increasing dietary fiber intake.

The influence of the dietary incorporation of Oatrim on gastrointestinal disturbance was investigated by Behall et al, (1998). They found that some abdominal discomfort and increased flatulence were reported when oat soluble fibers were incorporated into the diet. To determine the extent of gas production, hydrogen and methane were determined after the dietary incorporation. Hydrogen expiration was marginally increased, and was higher at 4, 5, and 6 hours after consuming the 10.2% β-glucan Oatrim (5.1-7.6 g from Oatrim and 5.9-8.4 g of oat β-glucan per day) versus the 1.6% β-glucan Oatrim (0.8-1.2 g from Oatrim and 1.6-2.0 g of oat β-glucan per day). Breath methane however, was not significantly different across the two Oatrim products.

Zarling et al, (1994) examined the effect of oat fiber consumption on bowel function and clinical tolerance when consumed in a tube-feeding situation *(it is unclear if this was soluble*

[9]See 1994-96, 1998 USDA Continuing Survey of Food Intakes by Individuals (CSFII) data found in Appendix 2, Environ Report: Estimated Intake of Fiber by Consumers of Products Proposed with Oatrim (BetaTrim™).

fiber, insoluble fiber or a ratio of the two). They employed a crossover study design to determine the effect of 28.8 g/day of 50% oat fiber and 50% soy fiber combination, among residents of a chronic care facility. It was found that over the 10-day intervention periods, the addition of the oat and soy fiber combination to tube feeding formulas was well tolerated, and promoted regular bowel movements without altering the rate of gastric emptying or intestinal transit time.

b) No Significant Adverse Effects on Vitamin and Mineral Absorption

Evidence to date, does not suggest that increased oat fiber consumption in general is likely to significantly affect mal-absorption of vitamins and minerals. Fat-soluble vitamins are absorbed similarly to triacylglycerol (i.e., they are dissolved in the lipid phase within the intestine, become incorporated into micelles for transportation and are ultimately absorbed by the intestinal mucosa). Due to the ability of certain dietary fibers to delay triacylglycerol absorption, it has been suggested that one might also see an altered absorption of fat-soluble vitamins. Long-term studies of vitamin A absorption have shown that wheat bran consumption can either increase (Rattan et al, 1981) or decrease (Wahal et al, 1986) serum vitamin A concentrations. Limited information exists on the influence of long-term consumption of specific fibers on other fat-soluble vitamin absorption. The studies that are available on the effect of fiber on fat-soluble vitamin absorption are inconsistent (Gallaher, 1999).

In general, the effect of fiber on absorption of water-soluble vitamins is even less understood than fat-soluble vitamins. Wheat bran has been shown to have no effect, and psyllium even appeared to increase riboflavin absorption at pharmacological doses (Roe et al, 1988). Studies on pectin fiber consumption have shown no negative effect on the utilization of vitamin B6 (Miller et al, 1980) or urinary ascorbic acid concentration (Keltz et al, 1978). Folic acid absorption was unaffected by wheat bran (Keagy et al, 1988).

The effect of various types and levels of dietary fiber on mineral absorption has also been examined. However, the results of these studies are inconsistent. To investigate the effect of oat bran muffins on calcium absorption and calcium, phosphorus, magnesium and zinc

balance, Spencer et al, (1991) conducted a strictly controlled metabolic balance study in adult male subjects. After a four-week adaptation period and a 40-day control period, the daily consumption of four oat bran muffins did not result in a change in calcium, magnesium and zinc balance, while nitrogen and phosphorus balance improved. Total dietary fiber intake increased from 22.6 g/day in the control period to 43.2 g/day in the oat bran period. The absorption or bioavailability of calcium, phosphorus, magnesium and zinc were not affected by the oat bran fiber intervention. The authors concluded that there would be no adverse effect on the nutritional status of these minerals if the American population were to increase intakes to reflect an oat bran fiber increase similar to the amounts used in their study.

Galibois et al, (1994) studied the effect of dietary fiber mixtures and different levels of these mixtures on mineral absorption in the rat. They investigated diets at 5 and 10% total dietary fiber from a mix of pectin and cellulose versus a mix of wheat bran and oat bran and a 5% cellulose only control. The apparent absorption of iron, zinc and magnesium was higher ($p < 0.05$) in rats fed the pectin-cellulose diets than those fed the wheat and oat bran diets. The fiber level affected only iron absorption. The authors of this study concluded that the source rather than the level of fiber in the diet might affect mineral absorption. However, the authors also pointed out that the apparent absorption of minerals in this study was calculated using mineral proportions in feces only. It is known that this method does not discriminate between unabsorbed dietary minerals and endogenous secretions.

Therefore, more research is necessary before any conclusions can be drawn concerning the effects of particular fiber types (including oat fibers) or fiber mixtures on mineral absorption. Although over the years the possibility that fiber consumption could impair mineral status has been raised many times, it has been argued persuasively by Gordon et al (1995) that evidence to support this contention is lacking. Overall, at present, there is no compelling evidence that consumption of oat fiber or concentrated sources of beta-glucan soluble fibers (such as Oatrim) significantly impair the absorption of vitamins or essential minerals in adequately nourished populations. Furthermore, there is a long history of consumption of fiber-rich foods but no major reports on vitamin-mineral mal-absorption

from high fiber consumption, therefore, it seems unlikely that one would observe serious effects from the estimated increase in fiber intakes from Oatrim (BetaTrim™) containing foods.

c) No Evidence of Adverse Effects from an Estimated Increase in Dietary Intakes of Total Fiber and Oat β-glucan from Proposed Addition of Oatrim (BetaTrim™)

The most recent national food consumption survey data—1994-96 USDA Continuing Survey of Food Intakes by Individuals (CSFII) and its Supplemental Children's Survey (CSFII 1998) was used to determine the estimated impact of Oatrim (BetaTrim™) on increased consumption of total dietary fiber and soluble fiber intake (Appendix 2). Beverages, bars and beverage mixes at a level of 0.75 g Oatrim (BetaTrim™) per serving were used in the analyses. Consumers of these product types were identified and the amounts of total dietary fiber and soluble fiber contributed by these products were estimated in the diets of these individuals. The mean total dietary fiber intake of users was 16.46 g before the addition of Oatrim (BetaTrim™). After addition of Oatrim (BetaTrim™), the estimated mean intake and the 90th percentile intake of total dietary fiber were 17.26 g and 28.9 g respectively. Mean total dietary fiber intakes with Oatrim (BetaTrim™) addition to foods, even at the 90th percentile of total fiber intake is estimated to be within the recommended 20-35 g range (NRC, 1989). Additionally, inclusion of Oatrim (BetaTrim™) foods will boost soluble fiber intake by about 5%. The petitioners conclude, that these small but beneficial dietary increases will not have any adverse effect, and that there is no indication that any special population or subset of the general population may be adversely affected by products containing β-glucan soluble fiber from Oatrim (BetaTrim™).

IV. NATURE OF THE SUBSTANCE AND FOODS ELIGIBLE TO BEAR THE CLAIM

The petitioner requests that the FDA approve Oatrim (BetaTrim™) on the basis of additional criteria beyond the preliminary criteria for health claims in 21 CFR 101.14, namely, the demonstration of sufficient intestinal viscosity to lower cholesterol (i.e., comparable to rolled

oats and oat bran) of Oatrim (BetaTrim™) processed by enzymatic and acid/base methods. The petitioners recommend this additional criteria based on scientific evidence that demonstrates not all processed soluble fibers are equally effective in their total- and LDL-cholesterol lowering potential and CHD risk. The effectiveness of the processed soluble fibers is largely determined by the processing method, the extent of processing employed, and after consumption at adequate levels, their ability to maintain sufficient intestinal viscosity.

A. IMPORTANCE OF PROCESSING METHOD TO VISCOSITY

When the FDA approved the health claim on the association of soluble fiber from rolled oats and reduced risk of heart disease (21 CFR 101.81) (62 FR 3584, January 23, 1997), the agency did not include or permit a claim for purified or isolated oat gums, or substances that were manufactured by different methods, or those not well defined chemically or physically. It is known that extensive processing, especially conditions that involve very high shear, may cause permanent loss in viscosity, a property that is closely associated with cholesterol lowering ability of processed soluble fibers. The relationship between processing and efficacy of the β-glucan soluble fiber was documented by Torronen et al (1992, *also cited in the original Quaker oat petition*). Torronen et al (1992) observed no significant cholesterol lowering effects between the oat and control intervention periods when a specially processed oat bran concentrate containing 15% β-glucan (dose: 11.2 g β-glucan) was incorporated into bread and evaluated in hypercholesterolemics for 8 weeks. The authors suggested that the wet milling and sieving in cold-water suspension method used to process this specially formulated oat bran concentrate made the β-glucan ineffective. They further stated that other studies conducted by the same investigative group indicated the weak effect of the β-glucan was probably attributed to its poor solubility, enzymatic hydrolysis after ingestion, and low viscosity in the intestine.

Oatrim (BetaTrim™), the focus of the current petition can be processed using two methods: an enzymatic or an acid/base method. Brief descriptions of these methods are provided in Appendices 1A & 1B. The Oatrim (BetaTrim™) ingredients produced from both processing methods have demonstrated bioequivalence relative to supernatant intestinal viscosity similar

to or greater than rolled oats and oat bran, using Gallaher's gut viscosity animal model (the same model discussed in comment C-1412, of the original Quaker oat petition, for the inclusion of whole oat flour). Furthermore, animal and human studies (see Section III, A-C) provide evidence of their cholesterol lowering properties, confirming that the above mentioned processing methods do not decrease the hypocholesterolemic properties of Oatrim (BetaTrim™).

Oatrim (BetaTrim™) -4, 12, and 20 % β-glucan concentration have been evaluated for their effectiveness using the intestinal contents supernatant viscosity method. All of these Oatrim (BetaTrim™) products demonstrated a supernatant intestinal viscosity sufficient to lower cholesterol as has been previously demonstrated with rolled oats and oat bran. The *in vivo* cholesterol-lowering potential of enzymatically processed Oatrim (BetaTrim™) was also evaluated in a rat chronic-feeding study. The Oatrim (BetaTrim™) ingredients utilized in Gallaher's recent studies (Freiburger & Gallaher, 2000; Freiburger & Gallaher, 2001; and unpublished work) discussed in Section III-C(2) of this petition, were processed by the enzymatic as well as the acid/base methods. Oatrim (BetaTrim™) at 12% and 20% β-glucan concentration were found to have absolute supernatant intestinal viscosities that were similar to and greater than rolled oats and oat bran, respectively. Oatrim (BetaTrim™)--at 1.6% and 10% β-glucan concentration and Oatrim (a processed oat bran concentrate) at 22.8% β-glucan have also been also shown to lower total- and LDL- cholesterol concentrations in humans (Behall et al, 1997; Pick et al, 1996). Based on the similarity in supernatant intestinal viscosity measures between Oatrim (BetaTrim™) from the enzymatic and the acid/base methods, the petitioner hereby concludes that the Oatrim (BetaTrim™) processed by the acid/base method would also produce a cholesterol reduction similar to that observed with enzymatically processed Oatrim (BetaTrim™).

B. DEFINITION OF BETA-GLUCAN SOURCE: OATRIM (BETATRIM™)

The petitioners hereby request the FDA to amend CFR 101.81 to include as a source of beta-glucan: Oatrim (BetaTrim™) with oat-β-glucan contents of a minimum 4% oat-β-glucan by weight to a maximum of 25% oat-β-glucan by weight. Manufacturing practices and natural

variation will produce a range of 4-6% β-glucan soluble fiber concentration for Oatrim (BetaTrim™) -5 and a range of 18-25% β-glucan soluble fiber concentration for Oatrim (BetaTrim™) -20. This range of oat-β-glucan content in Oatrim (BetaTrim™) is requested for inclusion in the soluble fiber health claim based on the data supporting their potential efficacy in reducing CHD risk (discussed in Sections III, A-C).

It is also important that the definition of eligible beta glucan source include starting materials described as "clean whole grain oat flour or oat bran." This precaution is a means of eliminating the use of oat flour and oat bran starting materials that include non-grain material from the dehulling process and or non-grain material from traditional oat-milling. The absence of hulls and the requirement of a minimum β-glucan soluble fiber concentration is very important to ensure that products labeled as "oat fiber," which are often made from oat hulls and are mostly insoluble fiber (and lack the physiological cholesterol lowering efficacy) do not assume eligibility.

C. Qualifying Levels of Beta-Glucan Soluble Fiber & Fiber Analysis

Section §101.81 of the health claim final rule established 3 g of β-glucan as the effective daily intake. This level has been previously established as the minimum daily intake to significantly lower cholesterol.

The 1997 oat health claim final rule indicated that the rolled oats, oat bran, and whole oat flour foods eligible to bear the claim were those that contained at least 0.75 g of soluble fiber per reference amount customarily consumed (RACC). This amount was determined by dividing 3 g of soluble fiber per day by four eating occasions per day. Oatrim (BetaTrim™) is a source of oat β-glucan and its bioequivalence has been established in this petition. Therefore, we propose that foods containing β-glucan soluble fiber from Oatrim (BetaTrim™) meet the same 3 g daily intake of β-glucan soluble fiber and 0.75 g of soluble fiber per RACC requirement of eligible food.

Expanding the claim to include Oatrim (BetaTrim™) increases the likelihood that physiologically effective sources of β-glucan soluble fiber will be incorporated into food products that presently cannot include sufficient amounts of rolled oats, whole oat flour, or oat bran to meet the minimum requirements of the health claim. Thus, many more foods with oats-β-glucan soluble fiber will be more readily available to the consumer, thereby increasing the likelihood of higher total and soluble dietary fiber consumption with a predictable reduction in heart disease risk.

Beta-glucan analysis as a marker, both for content and minimal efficacy of the Oatrim based eligible food products is necessary. The AOAC analytical method specified in §101.81 is applicable to the β-glucan from Oatrim, including Oatrim (BetaTrim™). Our experience with the analytical method is that the standard method, which is specific to the beta-linked-glucose polymers (Method 991.43; see Appendix 10), is suitable for products that contain β-glucan soluble fiber from Oatrim (BetaTrim™). Therefore, we are not providing a separate analytical method in this petition.

D. REPRESENTATIVE FOODS THAT MAY BEAR THE CLAIM

Current §101.81(c)(2)(iii) provides that the eligible food can include more than one of the whole oat sources of beta-glucan and that the whole oat foods must contain 0.75g of soluble fiber per reference amount customarily consumed of the eligible food. Quaker Oats and Rhodia Inc. propose the use of Oatrim (BetaTrim™) per reference amount for use in three [but not limited to] categories of food presented in Table 3. Eligible foods should also be allowed to contain Oatrim (BetaTrim™) in combination with the original whole oat sources of beta-glucan [e.g., whole oat flour plus Oatrim (BetaTrim™)], provided the combination of beta-glucan sources contributes 0.75 g soluble fiber to the eligible food.

Additionally, we recommend that food products eligible to bear the claim also be low in saturated fat, cholesterol and total fat and conform to the other health claim general principles (e.g., disqualifier levels).

Table 3: Some Uses of Oatrim (BetaTrim™)@

Food Category	Description of Foods	Serving Size	Soluble Fiber from Oatrim (BetaTrim™) per Serving
Bars	High protein bars, breakfast bars, meal replacement bars, granola bars, fortified high energy bars	40 g bar	0.75 g
Beverages	Milk analogues; milk-based fruit drinks, instant breakfast, diet and meal supplement/replacement beverages; citrus juices including grapefruit and orange juices and juice mixtures; tomato and vegetable juices; corn and bean beverages; cranberry juice drinks; fruit-flavored drinks	240 ml	0.75 g
Beverage Mixes	Milk analogue powders; milk beverage powders, instant breakfast, diet and meal supplement/replacement beverage mixes; protein powders and supplements; cereal beverage powders; fruit-flavored drink mixes	240 ml	0.75 g

@Listed are three examples of food categories.

E. PROJECTED IMPACT ON FOOD CONSUMPTION

A health claim for Oatrim (BetaTrim™) and CHD has the potential to increase the consumption of oat β-glucan soluble fiber, total soluble fiber, and total dietary fiber. To determine the estimated impact of Oatrim (BetaTrim™) on total dietary fiber and soluble fiber intake, Environ International was commissioned to conduct an analysis using the most recent national food consumption survey data from the1994-96 USDA Continuing Survey of Food Intakes by Individuals (CSFII) and its Supplemental Children's Survey (CSFII 1998) (Environ Report, see Appendix 2). The data is nationally representative and incorporates a sample of individuals (users) two years and older. Quaker Oats and Rhodia intend to market Oatrim (BetaTrim™) for use in selected bars, beverages, and beverage mixes at a level of 0.75 g Oatrim (BetaTrim™) per serving. Consumers or "users" of these product types were identified in the CSFII survey as those who reported consumption of a food from one of these

categories at least once during the two-day dietary intake recalls. The amounts of total dietary fiber and soluble fiber contributed by these products were estimated in the diets of these individuals before and after addition of Oatrim (BetaTrim™) (as the source of oat β-glucan soluble fiber). On the basis of the consumption patterns of the selected food categories, the mean intake of β-glucan from Oatrim (BetaTrim™) by the total population ranged from 0.54 g to 0.96 g per day per category and 0.80 g per day from all categories (Table 4).

The mean and 90th percentile total dietary fiber intakes of users were 16.46 g and 28.02 g, before the addition of Oatrim (BetaTrim™). After addition of Oatrim (BetaTrim™), the estimated mean intake and the 90th percentile of total dietary fiber were 17.26 g and 28.9 g respectively (Table 4). These data indicate that the consumption of Oatrim (BetaTrim™) fortified foods on a population basis, provides a beneficial, but conservative boost to overall total dietary fiber intake. Fiber intake even at the 90th percentile after Oatrim (BetaTrim™) addition is within the recommended range of 20-35 g per day (NRC, 1989).

The mean and 90th percentile of soluble fiber intakes of users was 5.81 g and 9.45 g respectively, before the addition of Oatrim (BetaTrim™). After addition of Oatrim (BetaTrim™), the estimated mean and the 90th percentile intake of soluble fiber were 6.61 g and 10.48 g, respectively. Currently there are no specific gram recommendations for soluble fiber intake. Inclusion of Oatrim (BetaTrim™) containing foods in the diet is expected to boost soluble fiber intake by about 5%. The majority of the increase in soluble fiber will be attributed to oat β-glucan soluble fiber. These small but beneficial increases in total and soluble fiber intakes from Oatrim (BetaTrim™) containing foods will provide the consumer with a better opportunity to incorporate the 3 g effective intake of oat β-glucan into the daily diet.

Table 4: Estimated Increase in Fiber Intake from Proposed Foods with Oatrim (BetaTrim™)

Environ Report: Table 9 (Reproduced from Appendix 2)

Soluble and Total Dietary Fiber Intake by Users of Products Containing Oat Soluble Fiber from Oatrim (BetaTrim™) Estimates of Intake Before and After Proposed Uses [a]

Total Population 2 years and older

	Before Proposed Uses						After Proposed Uses					
	Users [b]		Soluble Fiber		Total Dietary Fiber		Oat Soluble Fiber from Oatrim (BetaTrim™) [c]		Total Soluble Fiber [d]		Total Dietary Fiber [d]	
	Number of People [e]	Percent of People	Mean (g/d)	90th Percentile (g/d)	Mean (g/d)	90th Percentile (g/d)	Mean (g/d)	90th Percentile (g/d)	Mean (g/d)	90th Percentile (g/d)	Mean (g/d)	90th Percentile (g/d)
Bars	749	4.0	6.28	10.15	18.31	30.51	0.54	0.86	6.82	10.98	18.85	30.83
Beverages	5698	30.5	5.96	9.64	16.92	28.22	0.67	1.31	6.63	10.47	17.59	28.99
Beverage Mixes	2311	9.5	5.24	8.67	14.43	25.40	0.96	1.86	6.19	9.69	15.39	26.28
All Food Categories	7763	39.6	5.81	9.45	16.46	28.02	0.80	1.50	6.61	10.48	17.26	28.90

[a] Food consumption data source: 1994-96, 1998 Continuing Survey of Food Intakes by Individuals; estimates based upon 2-day average intakes per person. Fiber data source: ENVIRON and Nutrition Data System for Research (NDS-R) software version 4.02 (NCC, 1999). Proposed uses of Oatrim (BetaTrim™) provide 0.75g oat soluble fiber from Oatrim (BetaTrim™) per serving of food.

[b] A "user" of a food category was defined as an individual who reported consumption of a food from the category at least once during the two days of the 1994-96, 1998 CSFII diet recalls; "Number of People" represents the number of survey respondents who were users of the food category, and "Percent of People" represents the weighted proportion of individuals in this population group who were users of the food category.

[c] Reflects the oat soluble fiber provided by the proposed uses of Oatrim (BetaTrim™).

[d] Total soluble fiber and total dietary fiber estimates in the "After Proposed Uses of Oatrim (BetaTrim™)" scenario reflect the addition of oat soluble fiber provided by Oatrim (BetaTrim™).

[e] Mean estimates based on a sample size smaller than 75 and 90th percentile estimates based on a sample size smaller than 200 may tend to be less statistically reliable than estimates based on larger cell sizes (FASEB/LSRO, 1995).

V. HEALTH CLAIM EXAMPLES

Once Oatrim (BetaTrim™) is authorized to bear the health claim, the petitioners intend to use statements like the following for the claim. They are consistent with the model health claims currently in 21CFR 101.81. The petitioners request guidance as to whether such statements as these are acceptable.

A. Three grams per day of oat soluble fiber from Oatrim (BetaTrim™), as part of a diet low in saturated fat and cholesterol, may reduce the risk of coronary heart disease. This _____ (product) contains _____ grams per serving.

B. Three grams per day of oat beta-glucan soluble fiber daily from Oatrim (BetaTrim™), as part of a diet low in saturated fat and cholesterol, may reduce the risk of coronary heart disease. This _____ (product) contains _____ grams per serving.

C. Beta-glucan soluble fiber from Oatrim (BetaTrim™), as part of a diet low in saturated fat and cholesterol, may reduce the risk of coronary heart disease. This _____ (product) contains _____ grams per serving.

D. Diets low in saturated fat and cholesterol that include 3 grams per day of oat soluble fiber from Oatrim (BetaTrim™), may reduce the risk of heart disease. One serving of _____ (name of food) provides _____ grams of oat soluble fiber.

VI. ENVIRONMENTAL IMPACT

Quaker Oats and Rhodia Inc. claim a categorical exclusion under 21 CFR 25.32 (p) for an environmental assessment (EA) and environmental impact statement (EIS). Under the environmental impact consideration regulations, actions involving the issuance of a

health claim petition do not individually or cumulatively have a significant effect on the human environment; therefore, do not require the preparation of an EA or EIS.

VII. CONCLUSION

The information presented in this petition provides significant scientific evidence that the oat β-glucan soluble fiber from Oatrim (BetaTrim™), will reduce serum total- and LDL-cholesterol by clinically significant levels, thereby helping to reduce the risk of CHD in the U.S. population. The two manufacturing methods used by The Quaker-Rhodia Partnership to process and produce Oatrim (BetaTrim™) do not diminish the viscous properties and cholesterol-lowering efficacy of the oat β-glucan.

Rolled oats and oat bran were the subjects of Quaker Oats' original health claim petition, however, in the final rule, whole oat flour was included as an oat product eligible to bear the claim. In reviewing and approving the evidence submitted for the inclusion of whole oat flour, FDA noted the following (62 FR 3586, Jan. 23, 1997; Section II3):

- The similarity of whole oat flour to rolled oats in terms of chemical and physical properties and type of processing.
- Results of the human study evaluating whole oat flour on blood total- and LDL-cholesterol were consistent with the results of studies evaluating oat bran and rolled oats.
- Data from animal studies that demonstrate that whole oat flour retains viscosity characteristics during processing and digestion.
- Animal studies, which demonstrate bioequivalence relative to these important physical characteristics between whole oat flour and rolled oats.

The sections I-IV as detailed above, demonstrate that all of the criteria considered by FDA in including whole flour were met and exceeded for Oatrim (BetaTrim™). The β-glucan soluble fiber in Oatrim (BetaTrim™) is the same as that found in oat bran, rolled oats, and whole oat flour. Oatrim (BetaTrim™) is derived from the same starting material

as oat bran and whole oat flour. Although not identical in nutrient composition compared to rolled oats, whole oat flour and oat bran, Oatrim (BetaTrim™) β-glucan soluble fiber retains many of the physical and functional characteristics of the β-glucan in oat bran, rolled oats, and/or whole oat flour demonstrated by animal viscosity studies. Human studies and animal studies have shown that Oatrim (BetaTrim™) lowers serum lipids.

The positive dietary changes that will arise from the consumption of Oatrim (BetaTrim™) containing foods will result in substantial health benefits to the consumer, by specifically helping to reduce the risk of CHD in the U.S. population, and helping to decrease the growing economic burden attributed to CHD.

Therefore, Oatrim (BetaTrim™) should be approved for inclusion as an eligible source of oat β-glucan soluble fiber in 21 CFR 101.81.

VIII. PROPOSED REGULATION AMENDMENT

The petitioners recommend the following change to 21 CFR 101.81 to include the use of Oatrim (BetaTrim™) as a source of oat β-glucan soluble fiber eligible to bear the health claim.

21 CFR 101.81 (c)(2)(ii)(A) should be revised by adding a new subparagraph (*4*) as follows:

> (*4*) Oatrim (BetaTrim™). Oatrim (BetaTrim™), an oat-β-glucan soluble fiber concentrate produced by controlled enzymatic or acid/base hydrolysis of oat bran or whole oat flour that meets the criteria in subparagraph (c)(2)(ii)(A)(*1*) or (*3*) of this section. It contains 4 – 25% oat-β-glucan soluble fiber.

We, **Priscilla Samuel**, Ph.D., Senior Scientist and Director, Clinical Research Program, Nutrition Research & Services and **Robert Murray**, Ph.D., Director, The Gatorade Sports Science Institute & Quaker Nutrition, **The Quaker Oats Company**; and **James T. Elfstrum**, Manager, Regulatory Affairs, **Rhodia Inc.**, hereby certify that to the best of our knowledge this petition is a representative and balanced submission that includes unfavorable information as well as favorable information, known by the petitioners to be pertinent to evaluation of the proposed health claim.

Dated:

Yours very truly,

THE QUAKER OATS COMPANY

Priscilla Samuel, Ph.D.
Senior Scientist
Director, Clinical Research Program

Robert Murray, Ph.D.
Director
Gatorade Sports Science Institute
& Quaker Nutrition

AND,

RHODIA Inc.

James T. Elfstrum
Manager, Regulatory Affairs

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