

GRAS Notice (GRN) No. 434

<http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/GRASListings/default.htm>



**ORIGINAL SUBMISSION**

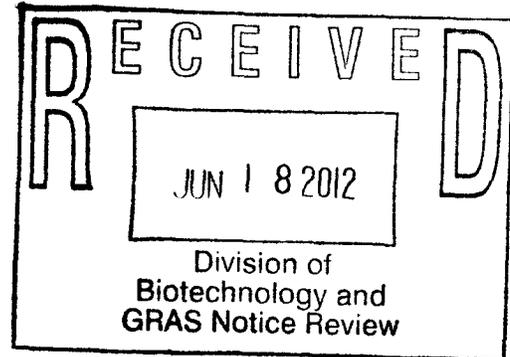
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# PHARMACHEM LABORATORIES

**phär-ma-foods**\*...efficacious food supplements standardized for specific potency, solubility, direct compression and disintegration characteristics...

June 12, 2012



Paulette Gaynor, Ph.D.  
Office of Food Additive Safety (HFS-200)  
Center for Food Safety and Applied Nutrition  
Food And Drug Administration  
5100 Paint Branch Parkway  
College Park, MD 20740-3835

Dear Dr. Gaynor:

In accordance with 21 CFR 170.36 (62 FR 18960; April 17, 1997), Pharmachem Laboratories, Inc. is hereby submitting notice of a claim that the use of a standardized extract of the common white bean (*Phaseolus vulgaris*) in foods is generally recognized as safe (GRAS) based on scientific procedures, and that it is therefore exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act.

Attached please find three (3) copies of the GRAS notice, each of which includes a comprehensive summary of data supporting the safety of the ingredients and the signed statement of an expert panel regarding the value of these data in supporting a GRAS determination.

My contact information is provided below. Please feel free to contact me<sup>1</sup> by phone or e-mail if you have any questions regarding this GRAS notice.

Sincerely,

(b) (6)

Carlos Irizarry, QA/QC

<sup>1</sup> Please note that Pharmachem Laboratories, Inc. has authorized Drs. David Bechtel ([David.Bechtel@Intertek.com](mailto:David.Bechtel@Intertek.com)) and Katherine Vega ([Katherine.Vega@Intertek.com](mailto:Katherine.Vega@Intertek.com)) from Intertek Cantox, located at 1011 U.S. Highway 22, Suite 200, Bridgewater, NJ 08827, to engage in discussions about any issues related to the enclosed GRAS notice. Each may be reached by e-mail (shown above), by telephone at (908) 429-9202, or by FAX at (908) 429-9260.

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# PHARMACHEM LABORATORIES

**phär-ma-foods**® ...efficacious food supplements standardized for specific potency, solubility, direct compression and disintegration characteristics...

## GRAS NOTICE

SUMMARY OF DATA SUPPORTING A DETERMINATION THAT THE USE OF AN EXTRACT OF THE COMMON WHITE BEAN (*Phaseolus vulgaris*) IN FOODS IS GENERALLY RECOGNIZED AS SAFE (GRAS)

**Submitted to:**

Food and Drug Administration  
Center for Food Safety and Applied Nutrition  
Office of Food Additive Safety

**By:**

Pharmachem Laboratories, Inc.  
265 Harrison Avenue  
Kearny, NJ 07032

June 12, 2012

## GRAS Exemption Claim

Pharmachem Laboratories, Inc. has determined with the assistance of qualified experts that the use of a standardized extract derived from the common white bean (*Phaseolus vulgaris*) in foods entails a reasonable certainty of no harm and is generally recognized as safe (GRAS) based on scientific procedures. Consequently, it is exempt from the premarket approval requirement of the Federal Food, Drug, and Cosmetic Act.

(b) (6)  
Signature 

Date 6/13/12

Carlos Irizarry, QA/QC

## Name and Address of Notifier

Pharmachem Laboratories, Inc.  
265 Harrison Avenue  
Kearny, NJ 07032

Contact Name: Carlos Irizarry  
Phone: 201-246-1000  
Fax: 201-246-8105  
E-mail: Clrizarry@pharmachemlabs.com

## GRAS Substance

The subject of this GRAS notice is a standardized dried aqueous extract derived from the common white kidney bean (*Phaseolus vulgaris*) marketed by Pharmachem Laboratories, Inc. primarily under the name Phase 2<sup>®</sup> (also as Phaseolamin 2250<sup>®</sup>, Phase 2 Starch Neutralizer<sup>®</sup>, Phase 2 Carb Controller<sup>®</sup> or StarchLite<sup>®</sup>). Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is manufactured using a proprietary variation of procedures widely used in the food industry and under current good manufacturing practices (cGMP) for human (21 CFR, part 110). Inspections and testing are performed at various points during the manufacturing process; every lot of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is tested for compliance with the established specifications (e.g., microbiological activity, heavy metals, and *in vitro* enzyme activity of at least 3000  $\alpha$ -amylase inhibiting units).

## Intended Use and Projected Consumer Exposure

Pharmachem intends to use Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract in foods for the general population at levels providing an aggregate intake of up to 10 g/person/day. Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract would be used as a substance offering nutritive value, based on its ability to inhibit the activity of the digestive enzyme  $\alpha$ -amylase *in vitro*, and the potential to interfere with carbohydrate digestion when taken with a meal by human subjects.

Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is intended for use in foods for healthy adults; it is not intended for use in infants or children.

## Basis for GRAS Determination

To make the GRAS determination, Pharmachem compiled information about the substance, specifications, manufacturing, proposed uses, and evidence of safety into a comprehensive dossier (GRAS Dossier); and sought the opinion of qualified experts (*i.e.*, expert panel) in determining whether there is consensus among their peers that the use of these substances as described entails a reasonable certainty of no harm and is generally recognized as safe based on the available scientific evidence.

All data and information that are the basis for this GRAS determination are available for FDA's review and copying at reasonable times at Pharmachem Laboratories, Inc., 265 Harrison Avenue, Kearny, New Jersey 07032, and will be sent to FDA upon request.



## **GRAS EXPERT PANEL STATEMENT**

**SUMMARY OF DATA SUPPORTING A DETERMINATION THAT  
THE USE OF AN EXTRACT OF THE COMMON WHITE BEAN  
(*Phaseolus vulgaris*) IN FOODS IS GENERALLY RECOGNIZED  
AS SAFE (GRAS)**

## EXPERT PANEL OPINION STATEMENT REGARDING THE USE OF AN EXTRACT OF THE COMMON WHITE BEAN (*PHASEOLUS VULGARIS*) IN FOODS AS GENERALLY RECOGNIZED AS SAFE (GRAS) BASED ON SCIENTIFIC PROCEDURES

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In the United States, a substance is exempt from the definition of “food additive” and thus from the premarket approval requirements outlined in section 201(s) of the Federal Food, Drug, and Cosmetic Act if its safety is generally recognized by qualified experts, *i.e.*, individuals qualified by scientific training and experience. A determination that the use of a substance is generally recognized as safe (GRAS) requires both technical evidence of safety (“technical element”) and a basis to conclude that this technical evidence of safety is generally known and accepted (“common knowledge element”), achieved most frequently through publication in peer-reviewed scientific journals.

A GRAS determination may rely on the recommendation of an authoritative body (*e.g.*, National Academy of Sciences) and/or the opinion of an “expert panel” specifically convened for this purpose. Accordingly, Pharmachem Laboratories, Inc. has requested of the undersigned experts an opinion regarding the GRAS status of a dried aqueous extract derived from the common white kidney bean (*Phaseolus vulgaris*), marketed primarily under the name Phase 2<sup>®</sup> (also as Phaseolamin 2250<sup>®</sup>, Phase 2 Starch Neutralizer™ or StarchLite™). Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is intended to be used in foods for the general population as a substance offering nutritive value, based on its ability to inhibit the activity of the digestive enzyme  $\alpha$ -amylase *in vitro*, and the potential to delay carbohydrate digestion. Pharmachem intends to use Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract in foods for the general population at levels providing an aggregate intake of up to 10 g/person/day.

To facilitate the review, each expert panel member received a dossier of data supporting the safety of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract and its status as a GRAS food ingredient. In making a determination regarding the GRAS status of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract, the panel considered that:

- The manufacturing process and product specifications have been standardized to ensure consistency in product composition and quality;
- Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is derived from the common white kidney bean, which has a long-time presence in the human diet. Raw or undercooked kidney beans naturally contain the anti-nutritive substances such as hemagglutinins (lectins) and trypsin inhibitors, which have been associated with adverse

effects in humans and other animals. These would be the substance of greatest toxicological concern. However, routine tests of production lots show that these substances are present at very low levels in Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract;

- Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract administered to rats in various oral (gavage) toxicity studies. No mortality or signs of toxicity were noted following administration of a single dose of the extract at up to 5000 mg/kg bw or multiple doses up to 2500 mg/kg bw/day for 28 days or up to 1112 mg/kg bw/day for 90 days.
- The effects of the enzyme  $\alpha$ -amylase are comparable across species, reducing the uncertainty regarding interspecies variability;
- The results of multiple clinical investigations in which hundreds of healthy subjects receiving Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (as is or as an ingredient in dietary supplements) at levels ranging from 500 to 3000 mg/day for periods from 30 days to 24 weeks showed no treatment-related adverse effects. While the primary objective of these studies was to assess the effects on glucose response and body weight loss, a subset of the studies included some measures of safety, such as hematology, clinical chemistry, and/or urinalysis; and
- Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is currently used in various forms (e.g., tablets, capsules, chewables, powdered drinks, chewing gums, baking mixes) in products marketed worldwide under approximately 200 brand names. These products provide up to 4500 mg/day (4.5 g/day) Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. To date, Pharmachem Laboratories, Inc. has had no reports of adverse events despite cumulative sale of 500,000 kg Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract.

### Expert Panel Opinion

An expert panel comprised of the undersigned members, qualified by scientific training and experience, has independently and critically evaluated the available information supporting the generally recognized as safe (GRAS) status of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. The extract is intended for use in foods for the general population at levels providing an aggregate intake of up to 10 g/person/day. Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is a substance offering nutritive value, based on its ability to inhibit the activity of the digestive enzyme  $\alpha$ -amylase *in vitro*, and the potential to delay carbohydrate digestion. The panel noted that Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is produced using processes consistent with current good manufacturing practices (cGMP) to comply with the specifications established by Pharmachem Laboratories, Inc.

Having considered all the available information, the undersigned members of the expert panel conclude that there is reasonable certainty that no harm will result from the use of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract as described and that such use may be considered GRAS based on scientific procedures.

<p><b>Robert J. Nicolosi, Ph.D.</b> Professor Department of Clinical Laboratory &amp; Nutritional Sciences University of Massachusetts Lowell Lowell, MA</p> <p>(b) (6)</p> <p>Signature: _____</p> <p>Date: <u>06 June 2012</u></p>	<p><b>Donald H. Hughes, Ph.D.</b> Hughes Consulting Cincinnati, OH</p> <p>(b) (6)</p> <p>Signature: _____</p> <p>Date: <u>6/14/12</u></p>
<p><b>David H. Bechtel, Ph.D., DABT (Facilitator)</b> Intertek Cantox Vice President, New Jersey Office Bridgewater, NJ</p> <p>(b) (6)</p> <p>Signature: _____</p> <p>Date: <u>June 15, 2012</u></p>	



## **GRAS DOSSIER**

**SUMMARY OF DATA SUPPORTING A DETERMINATION THAT  
THE USE OF AN EXTRACT OF THE COMMON WHITE BEAN  
(*Phaseolus vulgaris*) IN FOODS IS GENERALLY RECOGNIZED  
AS SAFE (GRAS)**

**Submitted to:**

Food and Drug Administration  
Center for Food Safety and Applied Nutrition  
Office of Food Additive Safety

**By:**

Pharmachem Laboratories, Inc.  
265 Harrison Avenue  
Kearny, NJ 07032

June 12, 2012

# Summary of Data Supporting a Determination that the Use of an Extract of the Common White Bean (*Phaseolus vulgaris*) in Foods is Generally Recognized as Safe (GRAS)

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# Summary of Data Supporting a Determination that the Use of an Extract of the Common White Bean (*Phaseolus vulgaris*) in Foods is Generally Recognized as Safe (GRAS)

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## 1.0 INTRODUCTION

### 1.1 Declaration of Intent

In the United States, substances added to food are exempt from the definition of “food additive” and thus from the premarket approval requirements outlined in section 201(s) of the Federal Food, Drug, and Cosmetic Act if their use is generally recognized as safe (GRAS). For substances not already on the list of GRAS substances<sup>1</sup> that are not considered harmful when added to food because of their intrinsic properties and/or because sufficient information about their safety exists, a proposed rule issued in 1997<sup>2</sup> provides a framework for self-determination of GRAS with the assistance of a panel of experts, *i.e.*, individuals qualified by scientific training and experience, specifically convened for this purpose. A determination that a substance is GRAS requires both technical evidence of safety and a basis to conclude that this technical evidence of safety is generally known and accepted. Self-determination of GRAS may be followed by notification to the Food and Drug Administration (FDA).

Pharmachem Laboratories, Inc., Pharmachem hereafter, has requested the assistance of Intertek Cantox in making a determination that the use of a dried aqueous extract derived from the common white kidney bean (*Phaseolus vulgaris*) marketed primarily under the name Phase 2<sup>®</sup> (also as Phaseolamin 2250<sup>®</sup>, Phase 2 Starch Neutralizer<sup>™</sup> or StarchLite<sup>™</sup>) in foods is GRAS based on scientific procedures. For the purposes of the present document, the name Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract will be used to refer to the substance under consideration.

Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is intended to be used in foods for the general population as a substance offering nutritive value, based on its ability to inhibit the activity of the digestive enzyme  $\alpha$ -amylase *in vitro*, and the potential to delay carbohydrate digestion. Alpha-amylase catalyzes the hydrolysis of complex carbohydrates into simpler saccharides such as maltose and glucose that can be absorbed. It is found in plants, animals, and microorganisms. Inhibition of human  $\alpha$ -amylase may hinder the digestion of complex carbohydrates. This may reduce the absorption of carbohydrate-derived calories, promoting or

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<sup>1</sup> 21 CFR 182—Substances generally recognized as safe; 21 CFR 184—Direct food substances generally recognized as safe; 21 CFR 186—Indirect food substances affirmed as generally recognized as safe.

<sup>2</sup> 62 FR 18938; April 17, 1997.

supporting weight loss. When taken by human subjects with a meal, Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract has been shown to moderate or decrease post-prandial blood glucose values compared to placebo. Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is intended for use at levels providing an aggregate intake of up to 10 grams per person per day (10 g/person/day).

The present document summarizes the available information supporting the safety of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. This includes consideration of the source material of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract, the common white kidney bean, and its long-time presence in the human diet as a (cooked) food item; the manufacturing process, established specifications, and demonstrated consistency in product quality; and the results of preclinical safety investigations and human studies showing, respectively, no toxicity in rodents exposed to oral doses up to 2500 mg/kg/day for 28 days or 1112 mg/kg bw/day for 90 days (maximum dose tested), or adverse health effects in subjects ingesting up to 3000 mg/day in divided doses with meals for periods from 30 days to 24 weeks. This information is intended to support a conclusion that there is consensus among qualified experts that there is reasonable certainty that the substance is not harmful under the intended conditions of use, and is therefore GRAS.

## **1.2 Background**

### **1.2.1 Dietary Carbohydrate Requirements and Intakes**

The Institute of Medicine (IOM) of the National Academy of Sciences has established a Recommended Dietary Allowance (RDA) of 130 g carbohydrates per day for adults and children, based on the average minimum amount of glucose utilized by the brain. The RDA is the intake that meets the nutrient needs of almost all (97% to 98%) individuals in a group. However, IOM recognized that this intake level is typically exceeded to meet the energy needs while consuming acceptable intake levels of fat and protein. The median intake of carbohydrates is reported to be about 200 to 330 grams per day for men and 180 to 230 grams per day for women (IOM, 2005).

### **1.2.2 Carbohydrate Digestion, Absorption, and Distribution**

The mechanisms by which carbohydrates are digested, absorbed, and distributed are well understood. Following ingestion, starches are converted by hydrolysis to glucose and other monomers that can be directly absorbed by the intestinal mucosa, or to oligosaccharides requiring further digestion prior to absorption. Absorption occurs by both passive diffusion and active transport mechanisms. Glucose, the final product of starch hydrolysis, is a common component in the human diet, as it constitutes an important source of energy. There are two main sources of starches in the human diet: naturally-occurring starches such as those found in

fruits, vegetables, cereals, and legumes, and processed (e.g., purified, refined) starches that are used in foods as thickeners, bulking agents, fillers, etc.

Starches vary greatly in their digestibility. Starches derived from roots (e.g., potatoes, legumes) are more difficult to digest than cereal starches. Processed, purified, and refined starches are easier to digest.

### 1.2.3 Alpha-Amylase

Alpha-amylase ( $\alpha$ -amylase) is an enzyme found in plants, animals, and microorganisms that catalyzes the hydrolysis of the  $\alpha$ -1,4-glycosidic linkages of starch molecules (i.e., amylose, amylopectin) into simpler saccharides such as maltose and glucose. In humans,  $\alpha$ -amylase is found in saliva and pancreatic extracts. Its release into the small intestine enables the hydrolysis of carbohydrates and subsequent absorption of glucose and related monomers by mucosal cells. The glucose monomers produced by the digestion of starch are an important source of cellular energy.

### 1.2.4 Alpha-Amylase Inhibition

Starch blockers are thought to promote weight loss by interfering with the digestion of complex carbohydrates through inhibition of  $\alpha$ -amylase, the digestive enzyme responsible for the breakdown of complex carbohydrates (i.e., starches) into simple sugars that can then be absorbed in the small intestine. The end result is a potential reduction in carbohydrate-derived calories.

Alpha-amylase inhibitors have been identified in many plant species. In 1943, Kneen and Sandstedt described the amylase-inhibiting activity of substances derived from wheat and rye, and certain sorghums. Bowman (1945) later found similar activity in simple aqueous extracts of ground navy beans. Since then,  $\alpha$ -amylase inhibitors have been isolated from various other plant species, including many varieties of the common (i.e., white, red, and black kidney) bean, *Phaseolus vulgaris* (Marshall and Lauda, 1975; Powers and Whitaker, 1977a, 1977b; Wilcox and Whitaker, 1984; Lajolo and Finardi-Filho, 1985).

The effect of purified isolate obtained from *P. vulgaris* has been well studied for its *in vitro* and *in vivo* capacity to inactivate amylase in the intestinal lumen. In healthy humans, clinical trials with  $\alpha$ -amylase inhibitors have been demonstrated to inhibit amylase and thereby reduce dietary starch digestion within the small intestine. In turn, decreased postprandial releases of insulin and gastric inhibitory polypeptide have been observed (Layer, *et al.*, 1985; Layer *et al.*, 1986a). The effects of  $\alpha$ -amylase inhibitors have also been demonstrated to substantially reduce postprandial increases in the plasma concentration of glucose and insulin in both normal and diabetic subjects (Layer *et al.*, 1986b; Boivin *et al.*, 1988). Moreover, when given in conjunction

with meals,  $\alpha$ -amylase inhibitors have proven effective in reducing carbohydrate absorption without causing gastrointestinal discomfort (Boivin, 1987).

### 3.0 MANUFACTURING AND PRODUCT SPECIFICATIONS

#### 3.1 Product Characterization

Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is manufactured by Pharmachem Laboratories, Inc. from raw white kidney beans derived from sources within the United States. They are distributor-certified as gluten-free and not genetically modified (non-GMO).

The physical and chemical characteristics of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract are summarized in Table 3-1. Table 3-2 provides typical nutritional information for the product.

**Table 3-1 Physical and chemical characteristics of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract**

<b>Trademark:</b>	Phase 2 <sup>®</sup> (also Phaseolamin 2250 <sup>®</sup> , Phase 2 Starch Neutralizer <sup>™</sup> , or StarchLite <sup>™</sup> )
<b>Common name:</b>	White Kidney Bean
<b>Botanical name:</b>	<i>Phaseolus vulgaris</i>
<b>Plant part:</b>	Seed
<b>Fresh/dry:</b>	Dry
<b>Native extract ratio:</b>	13:1 (11-15:1)
<b>Preparation type:</b>	Extract dry concentrate
<b>Final extract ratio:</b>	12:1
<b>Shelf life:</b>	2 years
<b>Sanitizing treatments:</b>	Not applicable
<b>GMO status:</b>	Non GMO
<b>Excipients:</b>	Not more than 10% Acacia
<b>Extraction solvent:</b>	100% water
<b>Storage conditions:</b>	Store in well sealed containers between 13 °C. Protect from light, moisture and heat
<b>Appearance:</b>	White to beige powder
<b>Odor:</b>	Characteristic
<b>Identification:</b>	Positive (FTIR)
<b>Moisture:</b>	<10% (Karl Fischer)
<b>Particle size:</b>	99% through US 60 mesh
<b>Heavy metals</b>	
<b>Lead</b>	<5 ppm (ICP)
<b>Arsenic</b>	<1 ppm (ICP)
<b>Mercury</b>	<1 ppm (AA)

**Table 3-1 Physical and chemical characteristics of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (Cont'd)**

<b>Microbiology:</b>	
<b>Total aerobic microbial count</b>	< 10 <sup>4</sup> org/g (USP/AOAC)
<b>Yeast and mould count</b>	< 10 <sup>2</sup> org/g (USP/AOAC/FDA-BAM)
<b>Coliform</b>	< 10 org/g (USP/AOAC)
<b><i>Escherichia coli</i></b>	Absent/g (USP/AOAC)
<b><i>Salmonella species</i></b>	Absent/10 g (USP/AOAC)
<b><i>Staphylococcus aureus</i></b>	Absent/g (USP/AOAC)
<b>Aflatoxins:</b>	< 5 ppb (Veratox)
<b>Pesticide residues:</b>	Complies with BP/EP/USP
<b>Residual solvents:</b>	Not applicable
<b>Assay:</b>	≥ 3000 alpha amylase inhibiting units (AAIU)/g (enzymatic Test Method Revision 5)

**Table 3-2 Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract nutritional information**

<b>Total Calories:</b>	Typically +/-330
<b>Calories from Fat:</b>	Typically LT 5
<b>Total Fat:</b>	Typically LT 0.5 g
<b>Saturated Fat:</b>	Typically 0.20 g
<b>Cholesterol:</b>	Typically LT 1.0 mgs
<b>Sodium:</b>	Typically 2,000 mgs.
<b>Total Carbohydrates:</b>	Typically 60 g
<b>Dietary fiber:</b>	Typically 3 g
<b>Sugars:</b>	Typically LT 4 g
<b>Protein:</b>	Typically 20 g
<b>Vitamin A:</b>	Less than 100 IU
<b>Vitamin C;</b>	Less than 1 mg.
<b>Calcium:</b>	Typically 250 mgs.
<b>Iron:</b>	Typically 4 mgs.

Approximate assay per 100 grams.

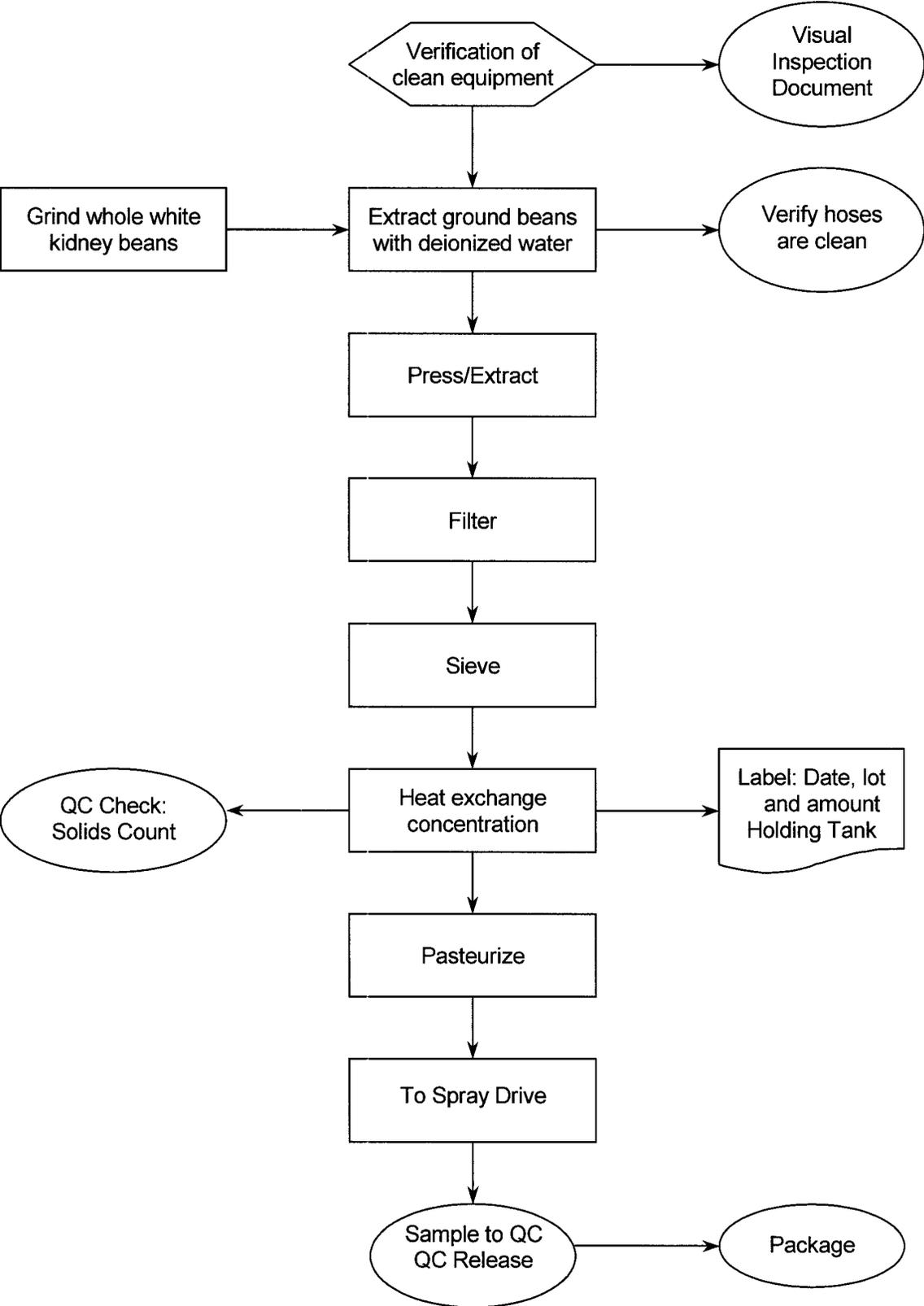
## 3.2 Manufacturing Process and Quality Control

Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is manufactured using a proprietary variation of procedures widely used in the food industry, as illustrated in Figure 3-1. The processing steps, the facility, and the controls used in the manufacture of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract are widely used in the food industry and conform to current good manufacturing practices (cGMP) for human food in accordance with the applicable parts of 21 CFR, part 110 of the Code of Federal Regulations. Inspections and testing are performed at various points during the manufacturing process. A visual inspection of the starting product, *Phaseolus vulgaris* white kidney beans, is performed prior to processing. All equipment is inspected for cleanliness and the results recorded in a Visual Inspection Document. A quality control check is performed following extraction and filtering for the solids content of native extract. At the end of processing, samples from 1 in 10 drums (50 kg drums) are collected for in-house microbiological analysis. Every lot of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is tested for microbiological activity (both in-house and by an independent laboratory), heavy metals, and *in vitro* enzyme activity (minimum 3000  $\alpha$ -amylase inhibiting units). Production lots of the extract are also regularly tested *in vitro* for hemagglutinating and trypsin inhibition activities. It is important to note that thermal processing conditions are employed that substantially inactivate anti-nutrient constituents naturally present in *Phaseolus vulgaris*, while substantially preserving  $\alpha$ -amylase inhibiting activity.

Table 3-3 provides the results of analysis of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract from three nonconsecutive batches (1009087890, 1107188738, 1203079596) by qualified laboratories. These batches were manufactured between September 2010 and March 2012. The test results indicate that all parameters measured were consistent with the established specifications.

The results of *in vitro* assays by Florida State University Department of Nutrition, Food and Exercise Sciences (FSU, 2004) for anti-nutritive substances (*i.e.*, hemagglutinins and trypsin inhibitors) naturally present in *Phaseolus vulgaris* are presented in Table 3-4. The hemagglutinin activity (HA) assay, which measures the ability of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract to agglutinate human erythrocytes, is based on methods described by Lis and Sharon (1972). Soybean lectin (Sigma Product No. L1395) was used as a positive control for hemagglutinin activity. The trypsin inhibitor activity (TIA) assay is based on methods approved by the American Association of Cereal Chemists (AACC, 1983). Defatted soybean flour was used as a positive control for trypsin-inhibiting activity.

**Figure 3-1 Overview of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract production method**



**Table 3-3 Results of analyses of multiple batches of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract**

Lot Number		(b) (4)	(b) (4)	(b) (4)	
Date of Manufacture		9/2010	7/2011	3/2012	
Date of Analysis		9/2010	8/2011	3/2012	
Parameter	Acceptance Criteria	Method	Test Results		
<b>Appearance:</b>	Free-Flowing Powder	Visual	Conform	Conform	Conform
<b>Color:</b>	Off-White to Beige	Visual	Conform	Conform	Conform
<b>Odor:</b>	Characteristic	Olfactory	Conform	Conform	Conform
<b>FTIR (Fourier transform infrared spectroscopy):</b>	Similar Spectrum to Std	FTIR	Pass	Pass	Pass
<b>Sieve Thru US 60 Mesh:</b>	Min. 99%	USP	99.80%	100%	100%
<b>Moisture:</b>	NMT (Not more than) 10%	LOD	5.55%	5.98%	4.89%
<b>Activity:</b>	NLT (Not less than) 3,000 Units/GM	PLAB.QC.TP20 Alpha Amylase Inhibitor Unit (AAIU)	5,100 units/gm	5,000 units/gm	3,900 units/gm
<b>Heavy Metals</b>					
<b>Lead:</b>	NMT 5 PPM	ICP-MS	LT 0.05	0.0593 PPM	0.066 PPM
<b>Arsenic:</b>	NMT 1 PPM		LT 0.05	LT 0.05 PPM	LT 0.05 PPM
<b>Mercury:</b>	NMT 1 PPM		N/D	0.024 PPM	LT 0.01 PPM
<b>Aflatoxin:</b>	NMT 5 PPB	Veratox	LT 5 PPB	LT 5 PPB	LT 5 PPB
<b>Pesticide:</b>	Complies to USP	USP	Complies	Complies	Complies
<b>Total plate count:</b>	NMT 10,000 CFU/GM	AOAC	LT 3,000 CFU/GM	LT 3,000 CFU/GM	LT 5,000 CFU/GM
<b>Yeast/Mold:</b>	NMT 100 CFU/GM	FDA-BAM	LT 100 CFU/GM	LT 100 CFU/GM	LT 100 CFU/GM
<b>Salmonella:</b>	Negative	AOAC	Negative	Negative	Negative
<b>E. coli:</b>	Negative	AOAC	Negative	Negative	Negative
<b>Staphylococcus:</b>	Negative	AOAC	Negative	Negative	Negative
<b>Coliforms:</b>		AOAC	LT 3/GM	LT 10/GM	LT 3/GM

**Table 3-4 Results of *in vitro* testing of 10 separate lots of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract for hemagglutinins and trypsin inhibitors**

Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract Lot No.	HU/g sample		TIU/mg sample		Moisture (%)		Proteins (g %)	
	A	B	A	B	A	B	A	B
0401273024	636	661	14.81	15.38	3.70	3.84	16.53	17.16
0311072910	160	171	15.98	17.15	6.78	7.27	11.57	12.41
0311072911	639	676	15.77	16.68	5.46	5.78	12.50	13.22
0311072912	319	339	15.91	16.92	5.95	6.33	11.58	12.31
0311072913	159	170	15.63	16.67	6.22	6.64	12.50	13.33
0401092984	641	679	16.64	17.64	5.69	6.03	12.75	13.52
0401092985	20	22	14.32	15.55	7.88	8.55	11.79	12.80
0401092986	639	681	17.50	18.66	6.21	6.62	10.86	11.58
0401092987	639	679	15.67	16.65	5.86	6.22	11.70	12.43
0401092988	320	341	18.83	20.12	6.42	6.86	12.51	13.36
<b>Controls</b>								
Defatted soybean flour	-	-	60.71	68.76	-	-	-	-
Lectin (soybean), Sigma (std)	32000	-	-	-	-	-	-	-

1. A = as is basis; B = dry weight basis.

2. Moisture analysis: as per AOAC method 32.1.03

3. Proteins (g%): soluble proteins extracted with Phosphate Buffer Saline (PBS), 0.01 M, pH 6.8.

4. One hemagglutinin unit (HU) defined as the least amount of hemagglutinin that produces positive evidence of agglutination. Hemagglutinating activity: defined by Sigma for lectins in *Glycine max*—Agglutinates a 2% suspension of fresh human blood group A erythrocytes at 31 µg lectin/mL after 1 h incubation at 25 °C. Activity determined from serial dilutions in 0.01 M phosphate buffered saline, pH 6.8, of a 1 mg/mL solution.

% activity: compared to soy lectin.

5. TIU = trypsin inhibitor units (based on absorbance at 410 nm).

## 4.0 CURRENT USES AND PROJECTED INTAKES

Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract has been and is presently used as an ingredient in various types of dietary supplements, including powders, tablets, capsules, and chewables. At present, there are approximately 200 brands of nutritional supplement products in the worldwide market that contain Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. A typical recommended supplement intake is 1 to 2 capsules, each containing 500 mg of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract, taken with each of 3 daily meals, adding up to 1500 to 3000 mg Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract per day. Table 4-1 lists several currently marketed products that contain Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract and the total daily intake of the extract based on the product manufacturer's recommended use. The maximum recommended daily intake of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract may reach 4500 mg. To date, Pharmachem Laboratories, Inc. has sold approximately 500,000 kg of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract over the past 5-6 years and has not received any reports of adverse events related to the extract.

Pharmachem intends to use Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract in foods for the general population at levels providing an aggregate intake of up to 10 g/person/day. Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract would be used as a substance offering nutritive value, based on its ability to inhibit the activity of the digestive enzyme  $\alpha$ -amylase *in vitro*, and the potential to interfere with carbohydrate digestion when taken with a meal by human subjects.

Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is intended for use in foods for healthy adults; it is not intended for use in infants or children.

**Table 4-1 List of marketed dietary supplement products containing Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract**

Company	Product	Amount of Phase 2 <sup>®</sup> White Kidney Bean ( <i>Phaseolus vulgaris</i> ) extract in Product	Recommended Use	Approximate Total Daily Intake of Phase 2 <sup>®</sup> White Kidney Bean ( <i>Phaseolus vulgaris</i> ) Extract
Leiner Health Products	Starch Away™	500 mg per piece	1-2 pieces before starchy meal	3000 mg
Metabolife International, Inc.	Starch Buster™	500 mg per tablet	2 tablets before starchy meal	3000 mg
Perrigo Company	Dr. Steven Rosenblatt's Ephedra Free Starch Blocker	500 mg per caplet	2 caplets before each meal	3000 mg
Natrol, Inc.	Carb Intercept™	500 mg per capsule	2 capsules with each carbohydrate containing meal	3000 mg
Naturade, Inc.	Diet Lean™ Carb Blocker	500 mg per tablet	2 tablets before starch-rich meal	3000 mg
Healthy Origins <sup>®</sup>	Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract Starch Neutralizer	500 mg per capsule	1-2 capsules before any starch-rich meal	3000 mg
General Nutrition Corporation	Complete with Phase2 <sup>®</sup>	500 mg per tablet	2 tablet prior to starch containing meal	1000 mg
Physicians Natural Products	Phase Away with Phase2 <sup>®</sup>	500 mg per capsule	1 capsule with meal	3000 mg
Now Foods	All Natural Phase2 <sup>®</sup>	500 mg per capsule	1 or 2 capsules before any meal containing complex carbohydrates or starches	3000 mg
Edge Labs	Carb Out	500 mg per 10.4g scoop	1 scoop with water just prior to meal	1500 mg
The Vitamin Shoppe <sup>®</sup>	Carb Tech™	250 mg per capsule	4 capsules daily	1000 mg
The Vitamin Shoppe <sup>®</sup>	Phaseolamin 2250™	500 mg per capsule	1 capsule before two largest meals	1000 mg
The Vitamin Shoppe <sup>®</sup>	Carb Shredder™	300 mg per tablet	1 tablet before two largest meals	600 mg
Puritan's Pride, Inc.	Xtreme Trim™	500 mg per tablet	2 tablets with every meal that contains carbohydrate	3000 mg
Swanson Health Products	Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract Starch Neutralizer	500 mg per capsule	2 capsules before each meal containing complex carbohydrates or starches	3000 mg

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**Table 4-1 List of marketed dietary supplement products containing Phase 2® white kidney bean (*Phaseolus vulgaris*) extract (Cont'd)**

Company	Product	Amount of Phase 2® White Kidney Bean ( <i>Phaseolus vulgaris</i> ) extract in Product	Recommended Use	Approximate Total Daily Intake of Phase 2® White Kidney Bean ( <i>Phaseolus vulgaris</i> ) Extract
Vitamin World, Inc.	Xtreme Trim™	500 mg per tablet	2 tablets with every meal that contains carbohydrates	3000 mg
Health Source, Inc.	Carb Extractor	500 mg per 3 capsules	3 capsules prior to each of the two largest meals	1000 mg
Dixie USA, Inc.	Phase 2® Starch Neutralizer	750 mg per scoop	Sprinkle 1 or 2 scoops on the first few bites of food at each meal	4500 mg
Doctor's A-Z™	Phase 2® Starch Neutralizer	500 mg per capsule	2 capsules before each meal containing complex carbohydrates or starches	3000 mg
NxGeneration	Carb Terminator	500 mg per capsule	2 capsules before eating a starchy meal	3000 mg
FoodScience Corp.	Carb Down™	500 mg per capsule	1 capsule before any meal containing carbohydrates from starch	1500 mg
MapleLeafRx	Carbotine	500 mg per tablet	1 tablet before meals that contain starch	1500 mg
Jarrow Formulas®	CarboTame™	500 mg per capsule	1-2 capsules before starchy meal	3000 mg
Liquid Health, Inc.	Carb Blocker	350 mg per capsule	2 capsules before each carbohydrate containing meal	2100 mg
Access Business Group, LLC	Nutrilite® Carb Blocker 2	500 mg per 3 tablets	1-3 tablets with a carbohydrate containing meal	1500 mg
HD Nutrition, Inc.	Carb Cheater™	500 mg per caplet	1-2 caplets with lunch and/or meal containing the most carbohydrates	2000 mg
Greenville Health Products	Phase 2®	500 mg per capsule	1-2 capsules before each meal	3000 mg
Source Naturals, Inc.	Carbohydrate Blocker	500 mg per tablet	2 tablets before a meal containing starch	3000 mg
Nature's Sunshine Products, Inc.	Carbo Grabbers™	300 mg per capsule	1-2 capsules before a meal high in carbohydrates	1800 mg
Biochem®	Carb Phaser 1000	225 mg per capsule	2 capsules before high carbohydrate meals	1350 mg

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**Table 4-1 List of marketed dietary supplement products containing Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (Cont'd)**

Company	Product	Amount of Phase 2 <sup>®</sup> White Kidney Bean ( <i>Phaseolus vulgaris</i> ) extract in Product	Recommended Use	Approximate Total Daily Intake of Phase 2 <sup>®</sup> White Kidney Bean ( <i>Phaseolus vulgaris</i> ) Extract
NEWtritional Health Care, LLC	Carb Control Ultra with Phase 2 <sup>®</sup>	500 mg per capsule	1-2 capsule prior to meal	3000 mg
National Vitamin Company	Starch Control <sup>™</sup>	500 mg per capsule	1-3 capsules prior to eating a meal containing carbohydrates	4500 mg
Prothera, Inc.	Thera-Slim <sup>™</sup>	500 mg per capsule	2 capsules before starch-rich meal	3000 mg
Optimum Nutrition	Diet Boost	500 mg per capsule	2 capsules before morning, afternoon and evening meals	3000 mg
Vitamer	Calorie Quencher <sup>™</sup>	1000 mg per 3 capsules	3 capsules at beginning of meals rich in carbohydrates	2000 mg
Health and Nutrition Systems International, Inc.	Carb Cutter <sup>®</sup>	500 mg per tablet	1-2 tablets with each of two largest carbohydrate meals	2000 mg
Sierra Medicinals, Inc.	Sierra Slim	500 mg per capsule	1-2 capsules before eating	3000 mg
LipoBan Clinic, Inc.	Carboban <sup>™</sup>	500 mg per capsule	1 capsule before lunch and dinner	1000 mg
LifeTime Nutritional Specialties, Inc.	Trim Down <sup>™</sup>	750 mg per tablet	1 tablet before high carbohydrate meals	2250 mg
Baywood International, Inc.	Carb Eliminator <sup>™</sup>	500 mg per capsule	1 capsule at mealtime	1500 mg
Leiner Health Products	Sprinkle packs with flavored Phase 2 <sup>®</sup> powder. Consumers to sprinkle on top of starchy foods such as baked potato, pasta, rice, cereal.	750 mg per tablet	1 packet per meal	2250 mg
Perrigo Company	Increased strength supplement	750 mg per packet	1 packet per meal	2250 mg

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## 5.0 SAFETY INFORMATION

### 5.1 Nonclinical Safety Studies of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract

#### 5.1.1 Overview

Table 5-1 provides a summary of toxicological studies of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract, and the sections below describe these studies in more detail.

The results of the nonclinical safety studies indicate that Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is of low toxicological concern. In rats, single oral doses of up to 5000 mg Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract per kg body weight did not result in any mortality or clinical signs of toxicity. Likewise, no adverse effects were observed in rats receiving Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract orally (gavage) at dosages up to 2500 mg/kg bw/day for 28 days or 1000 mg/kg bw/day for 90 days.

#### 5.1.2 Acute (Single-Dose) Oral Toxicity of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract in Rats

Harikumar *et al.* (2005) examined the acute oral toxicity of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract in rats.

Male and female Wistar rats (5/sex/group) received Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract by gavage as a single dose of 0, 500, 1000, or 5000 mg/kg bw (in 1 mL double distilled water as vehicle). Animals were monitored daily for 14 days for any clinical or behavioral symptoms, mortality, and adverse reactions. Food consumption and body weights were measured every third day. On Day 14, animals were sacrificed by vertebral dislocation. Blood samples were collected for hematological (total WBC, RBC, differential count, hemoglobin, platelets) and serum chemistry (SGOT, STPT, ALP, albumin, globulin, total protein, bilirubin, creatinine, urea, total HDL and LDL cholesterol, triglycerides, sodium, potassium, bicarbonate, chloride) analysis. Animals were examined visually for any abnormalities at necropsy; the weights of selected organs (liver, spleen, and kidney) were determined.

No mortality or adverse effects were noted in any of the animals. Body weight changes, food consumption, necropsy observations, organ weights, and hematological and serum chemistry parameters among rats receiving Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract were not significantly different from those of control animals. Histopathological examinations of the liver and kidneys revealed no remarkable findings.

Due to the absence of mortality at 5000 mg/kg, the highest dose tested, an oral median lethal dose (LD<sub>50</sub>) could not be established.

### 5.1.3 Subacute (28-Day) Oral Toxicity of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract in Rats

Chokshi (2007) examined the toxicity of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract in rats following oral (gavage) dosing for 28 days.

Eighty (80) young adult (7 to 8 weeks old) male and female Sprague-Dawley rats were acclimatized to the housing facilities for at least 5 days prior to being randomly assigned to the control or test groups (10/sex/group). For 28 consecutive days (7 days/wk), animals received Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (Lot # 0504063791) via oral gavage (10 mL/kg bw) at doses of 625, 1250, and 2500 mg/kg bw/day. Control animals received the vehicle control, distilled water. Animals were dosed at approximately the same time each day  $\pm$  2 hours. Animals were housed individually in stainless steel cages under standard animal room conditions; food and drinking water were given *ad libitum*.

Animals were monitored during the study for mortality, clinical signs, body weights, food consumption, hematology, and clinical chemistry. All surviving animals were euthanized by exsanguination from the abdominal aorta under isoflourane anesthesia. At necropsy, terminal body weights were obtained; organ to body weight ratios were calculated for liver, brain, spleen, kidneys, heart, ovaries and testes, adrenals, thymus, and epididymides. Samples of several organs and tissues were fixed and preserved in 10% neutral buffered formalin for histopathological examination. Histopathological examination of brain, spinal cord, lungs, trachea, thymus, heart, liver, salivary glands, sternum with bone marrow, adrenals, spleen, kidneys, thyroid/parathyroid, urinary bladder, ovaries, testes, uterus, vagina, and pancreas from control and high dose animals, and any animals that died during the study were performed.

The overall daily and weekly mean body weight and mean daily body weight gain for male and female rats at 625, 1250, and 2500 mg/kg bw/day were comparable with control values. Similarly, overall and mean daily food consumption and daily food efficiency for male and female rats in each dose group were comparable with control values.

There were no statistically significant treatment-related effects on hematology parameters. Higher platelet counts and a greater number of large unstained cells (white cells) were observed in females dosed with 1250 mg/kg bw/day. These statistically significant ( $p < 0.05$ ) but isolated changes in mean hematology results were considered to be non-adverse and unrelated to treatment. There were no treatment-related or statistically significant effects on coagulation parameters.

No treatment-related or statistically significant adverse effects on clinical chemistry parameters were observed. Mean cholesterol levels were significantly lower among females receiving 1250 mg/kg bw/day. However, this isolated effect was not considered to be related to treatment since it was not considered adverse *per se*, did not appear to be dose-related, and was not observed in males.

No gross abnormalities of toxicological significance were noted at necropsy. Isolated findings that were considered unrelated to treatment included: raised area on the liver in 1 male rat from the 1250 mg/kg bw/day group (discolored liver noted in 1 control male rat); distended uterus containing fluid in 2 females each from the 2500 mg/kg bw/day and control groups; and discolored material in the jejunum of 1 female each from the 1250 mg/kg bw/day female and 2500 mg/kg bw/day groups.

Mean absolute and relative organ weights (organ-to-body weight and organ-to-brain weight) were comparable to controls with the following exceptions: significantly lower mean kidney weight among males receiving 625 mg/kg bw/day (relative), and males receiving 1250 or 2500 mg/kg bw/day (absolute); significantly lower mean absolute adrenal weight in females at 2500 mg/kg bw/day. There were no microscopic or clinical pathology correlates to these findings in any of the collected organs. They were therefore considered to be of no toxicological significance.

Incidental microscopic findings in rats from both the control and treated groups included vacuolization in the adrenal cortex (males); myocardial degeneration in the heart (males); nephropathy (both sexes) and periportal hepatocellular vacuolization (females) in the liver; inflammation of the prostate (males); and dilatation of the uterine lumen (females). These changes are frequently observed in rats of this strain. In addition, there were generally no remarkable differences in the incidence of these lesions in the high-dose groups when compared to their respective controls. Consequently, they were not considered to be related to Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract administration.

Based on these observations, the no-observable-adverse-effect level (NOAEL) following oral (gavage) administration was considered to be the highest dose tested, 2500 mg/kg bw/day of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract.

#### **5.1.4 Subchronic (90-Day) Oral Toxicity of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract in Rats**

Harikumar *et al.* (2005) examined the subchronic oral toxicity of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract in rats.

Male and female Wistar rats (5/sex/group) received Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract by gavage at doses of 0, 200, 500, or 1000 mg/kg bw/day for 90 days (in 1.0 mL double distilled water as vehicle). Animals were monitored daily for mortality and signs of toxicity. Food consumption and body weights were measured every third day. On Day 90, animals were sacrificed by vertebral dislocation. Blood samples were collected for hematological (total WBC, RBC, differential count, hemoglobin, platelets) and serum chemistry (SGOT, STPT, ALP, albumin, globulin, total protein, bilirubin, creatinine, urea, HDL, LDL, triglycerides, sodium, potassium, bicarbonate, chloride) analysis. Animals were examined

visually for any abnormalities at necropsy. After weighing, portions of selected organs (liver, spleen, and kidney) were fixed and prepared for histopathological evaluation.

One male receiving 1000 mg/kg bw/day died after 21 days of treatment; however, the author did not indicate the cause of death. No signs of toxicity or weight changes were noted in this or any other animal receiving Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract, suggesting the death was not related to treatment. Body weight changes were comparable between control and treated rats. Animals treated with 1000 and 500 mg/kg bw/day of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract appeared to have consistently lower food consumption after Day 77. However, the relationship to treatment was unclear, especially since food spillage was not measured. Food consumption was determined by placing a known quantity of the feed in the cage and then weighing the remaining feed after 24 hours.

Some sporadic variations were noted in hematology and serum chemistry, but none reached statistical significance. There were no significant differences in the organ weights of animals treated with Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract compared to control. Histopathological examinations of the liver and kidneys revealed no remarkable findings.

Based on the results of this study, the no-observable-adverse-effect level (NOAEL) following oral (gavage) administration was considered to be the highest dose tested, 1000 mg/kg bw/day of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract.

**Table 5-1 Summary of nonclinical safety studies of Phase 2® white kidney bean (*Phaseolus vulgaris*) extract**

Reference	Study Type	Species/Strain	Dosage	Parameters Measured	Results
Harikumar <i>et al.</i> , 2005	Acute (Single-dose) Toxicity	Rat Wistar  5/sex/group	0 (vehicle control), 500, 1000, or 5000 mg/kg bw <i>via</i> gavage	Clinical signs, mortality, food consumption, and body weights over 14 days after a single dose; hematology, serum chemistry, organ weights, and histopathology of select organs (liver, kidneys) at study end.	LD <sub>50</sub> >5000 mg/kg bw  No mortality or toxicity. Comparable mean body weights, food consumption, necropsy observations, organ weights, and hematology and serum chemistry parameters between treated and control animals. No remarkable histopathological changes noted.
Chokshi, 2007	Subacute (28-day) Toxicity	Rat Sprague-Dawley  10/sex/group	0 (vehicle control), 625, 1250, or 2500 mg/kg bw/day <i>via</i> gavage	Clinical signs, mortality, food consumption, and body weights over 28 days; hematology, clinical chemistry, organ weights, and histopathology of select organs (all gross lesions, brain, spinal cord, thymus, adrenals, kidneys, ovaries/testes, uterus, vagina, lungs, trachea, salivary glands, sternum with bone marrow, heart, liver, spleen, urinary bladder, and thyroid/parathyroid) at study end.	NOAEL: 2500 mg/kg bw/day  No deaths or treatment-related effects on: clinical signs; body weights or nutrition; necropsy findings; clinical endpoints; or histopathological changes.
Harikumar <i>et al.</i> , 2005	Subchronic (90-day) Toxicity	Rat Wistar  5/sex/group	0 (vehicle control), 200, 500, or 1000 mg/kg bw/day <i>via</i> gavage	Clinical signs, mortality, food consumption, and body weights over 90 days; hematology, serum chemistry, organ weights, and histopathology of select organs (liver, spleen, and kidneys) at study end.	NOAEL: 1000 mg/kg bw/day  Death in 1 male in 1000 mg/kg bw/day group after 21 days. No clinical signs of toxicity noted. No statistically significant effects on body weights. Food consumption lower at 500 and 1000 mg/kg bw/day after Day 77, but the relationship to treatment was unclear. Sporadic variations in hematology and serum chemistry; no significant differences between in organ weights or histopathological findings.

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## **5.2 Nonclinical Safety Studies of Blokcal, a Dietary Supplement Product Containing Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract**

### **5.2.1 Overview**

Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is used as an ingredient in approximately 200 brands of nutritional supplement products marketed worldwide. Some of the dietary supplement manufacturers have shared the findings of their independent studies with Pharmachem. This information, summarized in Table 5-2, is included herein for completeness and as information corroborating the safety of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract.

Blockal is a dietary supplement distributed by ROEDER 1956 FARMACEUTICI, Italy. It contains 55.6% of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract, along with 20.3% calcium phosphate, 10.1% microcrystalline cellulose, 6.8% vitamin B<sub>3</sub>, and small quantities of other ingredients, including polyvinyl pyrrolidone (2.5%), silicone dioxide (2.0%), magnesium stearate (2.0%), vitamin B<sub>6</sub> (0.8%) and chromium picolinate (0.1%). Acute and subacute (28-day) oral toxicity studies of Blockal (Batch D106B) were conducted in Europe in accordance with Good Laboratory Practice (GLP) regulations<sup>3</sup>. The results of these studies showed no mortality or clinical signs of toxicity in rats following a single oral (gavage) dose of 3000 mg/kg bw of Blockal, providing 1668 mg/kg bw of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract). Likewise, no adverse effects were observed in rats receiving Blockal at 700 or 2000 mg/kg bw/day orally (gavage) for 28 days, equivalent to 389 and 1112 mg/kg bw/day of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract, respectively.

### **5.2.2 Acute (Single-Dose) Oral Toxicity Study of Blockal in Rats**

Chokshi (2006) examined the acute oral toxicity of Blockal, a dietary supplement containing 55.6% of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract, in rats.

Male and female Sprague-Dawley rats (5/sex/group) were monitored daily for 14 days following administration of a single oral (gavage) dose of 3000 mg/kg bw [providing 1668 mg/kg bw of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract].

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<sup>3</sup> Guidelines concerning Good Laboratory Practice (GLP) dated March 14, 2000, French Ministry of Social Affairs and National Solidarity, Official Text Reference MESP0020869A; Directive 87/18/EEC referring to Recommendation CC81/30, Appendix 2 of the OECD; OECD principles on GLP OECD Health and Safety publication ENV/MC/CHEM (98) 17 (as revised in 1997); GLP 21 CFR Part 58 Regulation dated December 22, 1978 and Amendments of April 11, 1980, September 4, 1987, and July 15, 1991, U.S. FDA; Good Laboratory Practice Guidelines: "notification No. 424 of the Pharmaceutical Affairs Bureau of the Japanese Ministry of Health and Welfare.

No mortality or clinical signs of toxicity were observed. Mean body weight gains were normal when compared with data for the strain. Necropsy examination revealed black spots on the thymus and lungs of one male. No other gross organ or tissue findings were observed.

The median lethal dose (LD<sub>50</sub>) was considered to exceed the highest dose of the Blockal supplement tested, 3000 mg/kg bw [1668 mg/kg bw of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract].

### **5.2.3 Subacute (28-Day) Oral Toxicity of Blockal in Rats**

Chokshi (2006) also examined the effects of Blockal administered orally to rats for 28 consecutive days.

For 28 consecutive days, male and female Sprague-Dawley rats (10/sex/group) received Blockal daily by oral gavage at dosages of 700 or 2000 mg/kg bw/day, providing 389 and 1112 mg/kg bw/day of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract, respectively. A similarly constituted control group received the vehicle, distilled water.

No mortality or clinical signs of toxicity were observed in any group during the study. Mean body weight gains and food consumption were unaffected by treatment. Terminal body weights were likewise unaffected. Compared to control animals, male rats receiving the Blockal supplement had significantly higher ( $p < 0.01$ ) serum total bilirubin (high- and low-dose) and creatinine (low-dose), and lower total cholesterol and calcium levels (both low-dose). High-dose males also showed a statistically significant increase in urine specific gravity when compared to controls. Females receiving Blockal exhibited significantly higher ( $p < 0.01$ ) red blood cell counts, hematocrit (high-dose), and total serum protein levels, along with lower total serum cholesterol levels (low-dose).

The most significant observation in the mean relative organ weights of male and female rats was a significantly higher ( $p < 0.01$ ) relative empty gut weights in both high-dose males and females compared to their respective controls. Other differences in organ weights that reached statistical significance at the  $p < 0.05$  level included lower absolute and relative liver weights, higher absolute and relative pancreas weights, and higher relative spleen weights, among high-dose males.

Although some variations were noted in the macroscopic (gross) and/or microscopic appearance of several organs and tissues, no statistically significant differences were noted between control animals and animals receiving the Blockal dietary supplement. Variations occurred in the gross appearance of liver, spleen, lungs, thymus, and uterus (filled with clear fluid). Of these, only the liver had corresponding microscopic changes, and the differences between control and treated animals were not statistically significant ( $p < 0.05$ ). Microscopic examination also revealed changes in the heart, kidneys, and skeletal muscle that were not

significantly different between groups. No changes were observed in the gross or microscopic appearance of the brain, cecum, colon, duodenum, ileum, jejunum, pancreas, rectum, spleen, or stomach of males or females.

In the absence of any relationship to dose and/or sex, or any corresponding histopathological changes, the variations observed in this study, which were also within the laboratory's historical values for this species, were not considered to be of toxicological significance. The 28-day no-observable-effect level (NOEL) in this study was equal to or greater than the highest dose of Blockal supplement tested (2000 mg/kg bw/day), which provided 1112 mg/kg bw/day of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract.

**Table 5-2 Summary of nonclinical safety studies of Blockal dietary supplement**

Reference	Study Type	Species/Strain	Dosage	Parameters Measured	Results
Chokshi, 2006.	Acute (Single-dose) Toxicity	Rat Sprague-Dawley  5/sex/group	0 (vehicle control) or 3000 mg/kg bw <i>via gavage</i> [0 or 1669 mg Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract]	Clinical signs, mortality, and body weights over 14 days; liver, spleen, kidneys, stomach, intestine, gonads/reproductive tract, lungs, and heart examined for gross findings at study end.	LD <sub>50</sub> >3000 mg/kg bw [1669 mg Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract].  No mortality or clinical signs of toxicity. Body weights unaffected by treatment. Black spots observed on thymus and lungs of 1 male; no other organ or tissue gross abnormalities seen.
	Subacute (28-day) Toxicity	Rat Sprague-Dawley  10/sex/group	0 (vehicle control), 700, or 2000 mg/kg bw/day  [0, 389, or 1112 mg/kg bw/day Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract]	Clinical signs, mortality, food consumption, body weights, hematology, clinical chemistry, urinalysis, organ weights, and histopathology of select organs (brain, cecum, colon, duodenum, heart, ileum, jejunum, kidneys, liver, pancreas, rectum, skeletal muscle, spleen, and stomach) at study end.	NOEL: 2000 mg/kg bw/day [1112 mg/kg bw/day of Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract]  No mortality or clinical signs of toxicity. Food consumption and body weights unaffected by treatment. Higher total serum bilirubin and creatinine in all animals, statistically significant only in males; significantly higher total protein, red blood cell count, and hematocrit (high-dose only) in females. Higher urine specific gravity in high-dose males. No effects on terminal body weights. Statistically significant differences in organ weights included: lower liver and pancreas weights (absolute and relative), and higher spleen weights (relative) in high-dose males; higher empty gut weights in males (absolute and relative) and females (relative).

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## **5.3 Clinical Studies of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract**

### **5.3.1 Overview**

Pharmachem Laboratories, Inc. has sponsored a series of exploratory clinical investigations employing Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. The studies, some of which have not been published, examined primarily the effects of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract on glucose response and body weight loss. Two studies included tests for hematology, clinical chemistry, and/or urinalysis [Udani and Singh, 2007; Udani *et al.*, 2004]. During these studies, Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract was administered to healthy subjects with meals as a single dose of up to 1.5 g, or in divided doses adding up to 3 g daily for up to 8 weeks. No effects of toxicological concern were observed in any of the Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract studies. These studies are summarized in Table 5-5 and described in more detail in subsequent sections.

### **5.3.2 Study of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract in Physically-Active Subjects (Pilot Study)**

A pilot study was conducted at the University of Scranton, Pennsylvania, to assess the effect of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract on glucose response following a carbohydrate-rich meal. After an overnight fast, 10 healthy male and female subjects (aged 21 to 57 years) were randomly assigned to receive 4 slices of white bread (60 g carbohydrates), 42 g soybean oil margarine, and 4 g Sweet'N Low sugar substitute, with or without 1.5 g Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. After treatment, subjects went about their normal daily activities, clerical or laboratory duties in this case. Plasma glucose was measured from blood samples drawn at baseline and every 30 minutes for 4 hours.

Subjects consuming the meal without Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract experienced an increase in blood glucose that peaked after 60 minutes. Subjects consuming the meal with Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract had a smaller increase than controls at 60, 90, and 120 minutes. Glucose clearance from plasma was also more rapid (~20 minutes) in subjects given Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. The area under the plasma glucose-time curve (a measure of glucose absorption and metabolism) was 57% lower in subjects taking Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. No side effects were observed (Vinson and Shuta, 2001a).

### **5.3.3 Study of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract in Physically-Inactive Subjects**

A second exploratory study conducted at the University of Scranton, Pennsylvania, assessed the effect of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract on glucose response following a carbohydrate-rich meal but, unlike the previous study in which subjects remained

physically-active, subjects in this study were required to rest between blood draws. After an overnight fast, 10 healthy male and female subjects (aged 21 to 27 years) were randomly assigned to receive 4 slices of white bread (60 g carbohydrates), 42 g soybean oil margarine, and 4 g Sweet'N Low sugar substitute with or without 1.5 g Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. Subjects were required to remain sedentary during the study. Plasma glucose was measured from blood samples drawn at baseline and for up to 2 hours, every 15 minutes for 1 hour, then every 20 minutes for the second hour. Two subjects failed to complete the study and 4 subjects were poor or nonabsorbers, as the area under the glucose-time curves were negative. Only data from the remaining 4 subjects were subjected to statistical analysis. The investigators did not specify how many of the remaining 4 subjects had received Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract.

Subjects consuming the meal without Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract experienced an increase in blood glucose that reached a broad peak after 45 minutes. Blood glucose concentrations in subjects treated with Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract peaked at 30 minutes. Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract treatment resulted in a smaller increase in blood glucose than the control from 15 to 80 minutes, with the greatest difference seen at 45 and 60 minutes, which approached but did not achieve statistical significance ( $p < 0.1$ ). Glucose clearance from plasma was also more rapid (~30 minutes) in subjects given Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. The area under the plasma glucose-time curve was 85% lower ( $p < 0.05$ ) in subjects taking Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (Vinson and Shuta, 2001b).

#### **5.3.4 Study of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract: Dose-Response After a Full Meal**

An exploratory study conducted at the University of Scranton, Pennsylvania, examined the effects of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract on glucose response after a full meal. After an overnight fast, 7 male and female subjects were randomly assigned to consume within 10 minutes 240 mL of water and a meal (Swanson Hungry-Man frozen dinner with 630 calories, 64 g carbohydrates, 29 g protein, and 29 g fat) consisting of country fried beef steak, gravy, mashed potatoes, green beans, and cherry-apple crumb dessert, with or without 0.75 g of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract added to the potatoes. Blood samples were obtained periodically over a period of 2 hours. Analyses of plasma glucose concentrations were performed by a certified clinical laboratory.

Compared to controls, subjects consuming the full meal with Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract had lower blood glucose levels at 10, 40, and 50 minutes. In subjects consuming Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract, plasma glucose levels reached baseline levels 12 minutes earlier than controls. The area under the plasma

glucose-time curve was 28% lower in subjects taking Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (Vinson, 2002).

### **5.3.5 Study of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract at Two Concentrations with a Full Meal**

An exploratory crossover study conducted at the University of Scranton, Pennsylvania, examined the effects of two Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract concentrations on glucose response after a full meal. After an overnight fast, 20 male and female subjects (aged 19 to 59 years) were randomly assigned to receive a standardized meal (Swanson Hungry-Man frozen dinner: meatloaf, gravy, mashed potatoes, green beans) containing 64 g of carbohydrates, 6 g fiber, and 19 g sugars, with: (1) 515 mg Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract; (2) 750 mg of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract; or (3) placebo. Blood glucose concentrations were measured from capillary (finger stick) blood samples using a One Touch<sup>®</sup> Ultra<sup>®</sup> monitoring system every 10 minutes for 1 hour. Over 3 weeks, subjects were assigned to receive a different treatment until all 3 products were tested.

The 750 mg concentration of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract produced lower blood glucose levels at 10, 20, and 30 minutes than either the 515 mg Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract concentration or placebo. The 515 mg concentration of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract produced lower blood glucose levels at 10, 20, and 30 minutes than the placebo. The area under the curve was lower following treatment with 750 mg Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract than with 515 mg Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract or placebo, but did not reach statistical significance (Vinson and Al Kharrat, 2003).

### **5.3.6 Study of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract in Overweight Adults**

A study was conducted at the Southern California University of Health Sciences to assess the effects of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract on body weight loss among overweight adults. For 30 days, 25 overweight adults (BMI  $\geq 23$  and  $\leq 31$  kg/m<sup>2</sup>) received a placebo or 1000 mg Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract twice a day before consuming starch-containing meals, along with changes in diet and exercise.

There was a time effect on body weight across all groups; weights decreased regardless of treatment as the study progressed. Some effects on subjective evaluations were noted. There were no significant differences between groups in the results of hematological screens before or at the end of the study. No side effects were reported during the trial (Udani and Singh, 2007).

### 5.3.7 Study of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract in Obese Adults

Udani *et al.* (2004) examined the effects of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract on body weight loss among obese adults. Thirty-nine obese subjects (BMI 30 to 43 kg/m<sup>2</sup>) were randomly allocated to receive either a placebo or 1500 mg of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract daily for 8 weeks. Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract was given with controlled high-fiber/low-fat meals (lunch and dinner) providing 100 to 200 g of complex carbohydrates per day (carbohydrate intake was recommended for each subject on the basis of estimated daily maintenance carbohydrate requirement).

Twenty-seven subjects completed all aspects of the study (14 test subjects and 13 placebo subjects). After 8 weeks, the Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract group lost an average of 3.79 pounds, while the placebo group lost 1.65 pounds. The decrease in triglyceride levels from baseline was more than 3 times as high in the Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract group as in the placebo group (26.3 mg/dL vs. 8.2 mg/dL decrease). Several secondary outcomes, including body fat percentage, waist and hip circumference, hunger, appetite, HbA<sub>1c</sub>, and total cholesterol were also measured, but no statistically significant differences between the Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract and placebo groups were noted. No adverse effects considered by the authors to be related to treatment were reported. One subject in the placebo group reported abdominal pain, bloating, and gas. One subject in the Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract group complained of an increased incidence of tension headaches.

The results of liver and kidney function test performed during this study were not included in the published article, but have been kindly provided by the authors for use in the present dossier. Tables 5-3a and 5-3b provide the initial results for the placebo and Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract groups, respectively; Tables 5-4a and 5-4b provide final results.

**Table 5-3a Initial biomarkers of liver and kidney function among subjects assigned to the placebo group\***

Patient ID	HGBA1C	GLU	BUN	Cr	Na	K	Cl	CO <sub>2</sub>	Ca	TP	ALB	AST	ALT	ALKP	BILI total
3	5.2	95	10	0.7	141	4.4	103	29	9.2	7.7	3.9	25	17	76	0.4
2	5.3	95	14	0.8	143	4.3	102	30	8.9	8	4	60	53	121	0.2
4	5.3	86	16	1	142	4	103	30	8.7	7.4	4.1	32	33	72	0.5
11	5.4	111	13	0.7	140	4	104	25	8.4	7.8	3.9	34	38	87	0.1
15	5.4	107	35	1	141	4	100	30	8.8	7.9	3.9	49	39	94	0.1
7	5.7	84	7	0.8	139	4.2	101	29	8.6	7.8	3.7	44	12	84	0.1
19	5.4	85	13	0.8	142	4.5	102	31	9.5	8.5	4	48	38	186	0.5
23	5.9	106	9	0.8	142	4.2	108	27	8.3	7.2	3.5	50	21	62	0.3
27	5.6	101	18	0.8	142	4.5	105	28	8.9	7.4	3.9	33	30	76	0.4
32	5.4	90	13	0.7	141	3.7	104	27	8.2	7.6	4	26	18	83	0.3
1	5.7	107	20	1	143	4.1	108	27	8.8	7	3.9	20	18	62	0.1
10	6.8	121	12	0.8	145	4.1	105	27	9.2	7.8	4	31	26	123	0.2
28	5.3	95	12	0.8	144	4	108	27	8.7	7.5	3.8	42	24	91	0.2
<b>Mean</b>	5.57	98.69	14.77	0.82	141.92	4.15	104.08	28.23	8.784	7.664	3.894	38	28.23	93.62	0.26
<b>STD</b>	0.42	11.28	7.01	0.11	1.61	0.23	2.66	1.74	0.374	0.384	0.16	11.76	11.62	33.53	0.150

\* Unpublished data from Udani *et al.*, 2004.

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**Table 5-3b Initial biomarkers of liver and kidney function in subjects assigned to the Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract group\***

Patient ID	HGBA1C	GLU	BUN	Cr	Na	K	Cl	CO <sub>2</sub>	Ca	TP	ALB	AST	ALT	ALKP	BILI total
12	5.7	103	13	0.9	142	4.6	106	27	8.8	7.1	3.7	20	16	59	0.1
13	6.2	121	9	0.6	141	4.3	100	30	9.3	8.7	4	55	61	104	0.5
18	6	115	22	0.8	141	4.8	103	28	8.6	7.6	4	23	38	94	0.2
20	6.5	117	15	0.8	141	4.1	109	23	8.5	7.3	3.4	32	28	78	0.4
21	5.5	87	11	0.9	145	3.9	107	28	9.4	7.5	4.1	24	26	67	0.1
29	5.9	101	25	1.2	143	4.4	103	29	8.7	7.8	4.1	31	56	71	0.6
30	5.6	91	8	0.7	142	4.5	104	29	9.4	7.4	3.9	19	19	66	0.4
31	5.8	94	13	0.7	144	4.2	109	26	9	7.6	3.8	31	37	95	0.3
8	5.2	84	11	0.7	140	4.3	105	26	9	7.3	3.8	21	16	84	0.5
49	5	99	8	0.7	142	4.2	104	26	8.7	8.2	3.8	23	21	79	0.8
38	5.5	100	9	0.8	141	4.4	102	29	9.1	7.8	3.9	30	34	93	0.4
42	5.4	92	15	1	142	4.7	103	30	9.6	7.7	4	25	24	57	0.1
47	5.5	99	18	1.1	142	4.3	103	29	8.9	7.3	4.3	22	21	71	1
48	4.9	97	9	0.8	141	4.1	103	27	9.4	7.8	4.2	16	15	58	0.3
<b>Mean</b>	5.62	100	13.29	0.84	141.9	4.34	104.4	27.64	14.62	7.65	3.93	26.57	29.43	76.86	0.41
<b>STD</b>	0.44	11.03	5.28	0.17	1.33	0.25	2.59	1.95	20.83	0.42	0.23	9.56	14.46	15.27	0.26

\* Unpublished data from Udani *et al.*, 2004.

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**Table 5-4a Final biomarkers of liver and kidney function among subjects receiving placebo for 8 weeks\***

Patient ID	HGBA1C	GLU	BUN	Cr	Na	K	Cl	CO <sub>2</sub>	Ca	TP	ALB	AST	ALT	ALKP	BILI total	Blood Urea Nitrogen	Globulin	A:G Ratio
3	4.6	99	37	0.6	138	4.2	101	26	9.2	7.4	4	13	12	89	0.4	22	3.4	1.2
2	5.3	106	19	0.9	139	4.5	98	30	9.4	7.3	4.2	32	35	123	0.4	17	3.1	1.4
4	5	107	17	1	141	4	100	31	9.5	6.9	4.6	23	24	71	0.7	17	2.3	2
11	4.9	109	16	0.8	137	4.2	101	26	10.1	7.3	4.3	24	23	79	0.5	13	3	1.4
15	5	119	15	1.1	138	4.1	98	27	10.1	7.9	4.4	27	29	95	0.6	17	3.5	1.3
7	4.4	97	17	0.9	142	4.1	103	29	9.3	7.2	4.2	19	23	65	0.7	17	3	
19	5	103	15	0.8	138	3.8	101	26	10	7.8	3.9	42	40	165	0.6	12	3.9	1
23	5.5	120	9	0.7	140	3.8	103	27	8.6	6.6	4.1	18	11	53	0.5	6	2.5	1.6
27	5.4	108	20	0.8	140	3.8	102	26	9.4	7.1	4.4	22	19	72	0.5	16	2.7	1.6
32	5.1	96	20	0.7	141	3.8	103	27	9.5	7.4	4.5	15	15	80	0.4	14	2.9	1.6
1	5.3	107	24	0.9	145	4.4	104	27	9.4	7.1	4.8	17	16	81	0.3	22	2.3	2.1
10	6.5	126	18	0.8	142	3.6	98	29	9.7	7.2	4.3	23	20	127	0.4	14	2.9	1.5
28	4.9	103	16	0.7	140	3.4	102	26	9.3	7.2	4.2	15	13	91	0.4	11	3	1.4
<b>Mean</b>	5.15	107.69	18.69	0.82	140.08	3.98	101.08	27.46	9.5	7.26	4.3	22.301	21.54	91.612	0.49	15.23	2.96	1.51
<b>STD</b>	0.51	9.09	6.51	0.14	2.18	0.31	2.06	1.71	0.41	0.34	0.24	7.95	8.88	30.35	0.13	4.34	0.46	0.31

\* Unpublished data from Udani *et al.*, 2004.

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**Table 5-4b Final biomarkers of liver and kidney function among subjects receiving Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract for 8 weeks\***

Patient ID	HGBA1C	GLU	BUN	Cr	Na	K	Cl	CO <sub>2</sub>	Ca	TP	ALB	AST	ALT	ALKP	BILI total	Blood Urea Nitrogen	Globulin	A:G Ratio
12	5	90	15	0.8	139	4.3	102	26	9.6	6.9	4.2	25	27	52	0.4	12	2.7	1.6
13		138	20	0.6	137	4.6	98	27	9.6	7.6	4	30	41	94	0.6	12	3.6	1.1
18	5.5	110	28	0.6	136	4.6	99	27	8.9	7.4	4.1	20	38	104	0.6	17	3.3	1.2
20	5.7	130	21	0.7	137	4.7	101	24	9.1	7.1	3.6	32	31	92	0.5	15	3.5	1
21	5.1	92	16	0.7	139	3.9	102	22	9.3	7.5	4.6	17	18	71	0.5	11	2.9	1.6
29	5.6	107	17	1.1	142	4	104	29	9.4	7.1	4.5	14	28	62	0.6	19	2.6	1.7
30	5	100	23	0.6	140	4.3	104	26	9.3	6.8	4.3	15	17	60	0.5	14	2.5	1.7
31	5.4	97	21	0.8	141	4.2	105	23	10.1	7.3	4.6	23	33	90	0.5	17	2.7	1.7
8	5	84	15	0.6	139	3.9	101	27	9.6	7.2	4.1	13	10	80	0.8	9	3.1	1.3
49	4.8	113	10	0.7	140	4.4	101	25	9.5	7.4	4.2	15	18	82	0.6	7	3.2	1.3
38	4.6	109	23	0.7	141	5.3	102	25	10	7.9	4.5	24	25	88	0.4	16	3.4	1.3
42	5.1	78	16	0.9	138	4.1	99	27	10.3	7.3	4.6	18	21	67	0.4	14	2.7	1.7
47	5.2	103	20	1	142	4	103	30	9.4	7.1	4.7	13	17	61	1	20	2.4	2
48	4.7	101	23	0.8	138	4.2	99	26	9.8	7.3	4.6	16	14	58	0.4	18	2.7	1.7
<b>Mean</b>	5.6	103.7	19.14	0.76	139.2	4.32	101.4	26	9.56	7.28	4.33	19.64	24.14	75.79	0.56	14.36	2.95	1.49
<b>STD</b>	5.3	16.34	4.59	0.16	1.89	0.38	2.14	2.15	0.39	0.28	0.31	6.23	9.26	16.26	0.17	3.82	0.39	0.29

\* Unpublished data from Udani *et al.*, 2004.

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### **5.3.8 Study of the Effects of Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*) Extract on the Glycemic Index of White Bread Consumed by Adults**

Udani *et al.* (2009) examined whether the addition of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract to white bread would lower its glycemic index (GI). An open-label 6-arm crossover study was conducted with 13 randomized subjects between the ages of 24 and 44 and a body mass index (BMI) between 18 and 25 kg/m<sup>2</sup>. In order to standardize the glycemic response on each study test day, subjects were required to consume only a diet of standardized prepared low-fiber frozen foods containing a minimum of 100 g of carbohydrates. Subjects reported to the study center 7 times to receive 50 g net carbohydrates in the form of white bread with butter. Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract was administered at 1500 mg, 2000 mg, and 3000 mg, either in capsule or powder form. The powder form of the test product was mixed into the butter that was spread on the bread. The capsules were taken immediately prior to the ingestion of food. The white bread was consumed within 5 minutes and the only beverage allowed during the testing session was ice water. The test meals were administered in a random order and test visits were less than 2 weeks apart.

Capillary blood was analyzed for blood glucose and was drawn twice at baseline and then at times 0 (start of meal), 15, 30, 45, 60, 90, and 120 minutes. Statistical analysis was performed by one-way analysis of variance (ANOVA) using unadjusted multiple comparisons (t tests) to the white bread control. There was an apparent dose-related effect of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract on the GI response to white bread with both powder and capsule formulations. For the capsule formulation, the 1500 mg dose had no effect on the GI and the 2000 mg and 3000 mg capsule doses caused insignificant reductions in GI. For the powder, the 1500 mg and 2000 mg doses caused insignificant reductions in the GI, and the 3000 mg dose had a significant effect. The authors reported that all of the dosages and formulations appeared to be well tolerated, and no adverse events were observed or reported during the study.

**Table 5-5 Summary of clinical investigations of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract**

Reference	Number of Subjects Enrolled	Treatment	Duration	Parameters Measured	Results
Vinson and Shuta, 2001a (Unpublished)  University of Scranton, PA, September 2001	10 healthy adults	Single meal consisting of 4 slices white bread (60 g carbohydrates), 42 g soybean oil margarine, and 4 g Sweet'N Low sugar substitute, with or without 1.5 g Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract. Subjects remained physically active during study.	Single dose	Plasma glucose was measured at baseline and every 30 minutes for 4 hours	Subjects consuming the meal without Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract experienced an increase in blood glucose that peaked after 60 minutes. Subjects consuming the meal with Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract had a smaller increase than controls at 60, 90, and 120 minutes. Glucose clearance from plasma was more rapid (~20 minutes) and the area under the plasma glucose-time curve was 57% lower in subjects given Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract. No side effects were observed.
Vinson and Shuta, 2001b (Unpublished)  University of Scranton, PA, November, 2001	10 healthy adults  <u>NOTE:</u> 2 subjects failed to complete the study and 4 subjects were poor or nonabsorbers, as the area under the glucose-time curves were negative. Therefore only data from the remaining 4 subjects were subjected to statistical analysis.	Single meal consisting of 4 slices white bread (60 g carbohydrates), 42 g soybean oil margarine, and 4 g Sweet'N Low sugar substitute, with or without 1.5 g Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract. Subjects rested between blood draws.	Single dose	Plasma glucose was measured at baseline and every 15 minutes for 1 hour, then every 20 minutes for another hour.	Subjects consuming the meal without Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract experienced an increase in blood glucose that reached a broad peak after 45 minutes. Blood glucose concentrations in subjects treated with Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract peaked at 30 minutes. Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract treatment resulted in a smaller increase in blood glucose than the control from 15 to 80 minutes, with the greatest difference (p<0.1) seen at 45 and 60 minutes. Glucose clearance from plasma was also more rapid (~30 minutes) in subjects given Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract. The area under the plasma glucose-time curve was 85% lower (p<0.5) in subjects taking Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract. It was not clear whether subjects were monitored for adverse events.

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**Table 5-5 Summary of clinical investigations of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (Cont'd)**

Reference	Number of Subjects Enrolled	Treatment	Duration	Parameters Measured	Results
Vinson , 2002 (Unpublished)  University of Scranton, PA, May, 2002	7 healthy adults	Single meal (Swanson Hungry-Man frozen dinner with 630 calories, 64 g carbohydrates, 29 g protein, and 29 g fat) consisting of country fried beef steak, gravy, mashed potatoes, green beans, and cherry-apple crumb dessert, with or without 750 mg Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract added to the potatoes, and 240 mL of water.	Single dose	Blood samples were obtained periodically over a period of 2 hours. Analyses of plasma glucose concentrations were performed by a certified clinical laboratory.	Compared to controls, subjects consuming the full meal with Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract had lower blood glucose levels at 10, 40, and 50 minutes. In subjects consuming Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract, plasma glucose levels reached baseline levels 12 minutes earlier than controls. The area under the plasma glucose-time curve was 28% lower (p<0.5) in subjects taking Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract. It was not clear whether subjects were monitored for adverse events.
Vinson and Al Kharrat, 2003 (Unpublished)  University of Scranton, PA, September, 2003	20 healthy adults	Single meal (Swanson Hungry-Man frozen dinner: meatloaf, gravy, mashed potatoes, green beans) containing 64 g of carbohydrates, 6 g fiber, and 19 g sugars, with: 1) 515 mg Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract; 2) 750 mg of Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract; or 3) placebo.  Over 3 weeks, subjects were assigned to receive a different treatment until all 3 products were tested.	Single dose	Blood glucose concentrations were measured from capillary (finger stick) blood samples using a One Touch <sup>®</sup> Ultra <sup>®</sup> monitoring system every 10 minutes for 1 hour.	The 750 mg concentration of Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract produced lower (p<0.01) blood glucose levels at 10, 20, and 30 minutes than either the 515 mg Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract concentration or placebo. The 515 mg concentration of Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract produced lower blood glucose levels at 10, 20 (p<0.01), and 30 minutes (p<0.05) than the placebo. The area under the curve was lower following treatment with 750 mg Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract than with 515 mg Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract or placebo, but did not reach statistical significance. It was not clear whether subjects were monitored for adverse events.

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**Table 5-5 Summary of clinical investigations of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (Cont'd)**

Reference	Number of Subjects Enrolled	Treatment	Duration	Parameters Measured	Results
Udani and Singh, 2007.	25 Overweight adults (BMI $\geq 23$ kg/m <sup>2</sup> and $\leq 31$ kg/m <sup>2</sup> )	Placebo or 1 g Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract twice a day before starch-containing meals in combination with diet and exercise.	30 days	Hematological screen performed at baseline and at the end of the study. Body weights and body fat composition were determined at baseline and weekly thereafter. Subjective evaluations of hunger, energy, and appetite were collected.	There was a time effect on body weight across all groups; weights decreased regardless of treatment as the study progressed. Some effects on subjective evaluations were noted. There were no significant differences between groups in the results of hematological screens before or at the end of the study. No side effects were reported during the trial.
Udani et al., 2004	39 Obese adults (BMI of 30 to 43 kg/m <sup>2</sup> )  <u>NOTE:</u> 50 subjects were screened, 39 were randomized, and 27 completed the study.	Subjects were randomly allocated to receive a placebo or 1.5 g Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract twice daily with controlled high-fiber/low-fat meals providing 100 to 200 g complex carbohydrates per day for 8 weeks.	8 weeks	Measurements included body weights, body fat composition, blood glucose, triglycerides, cholesterol, liver/kidney function (serum creatinine and BUN), hemoglobin A <sub>1c</sub> , hematology, and/or urinalysis at baseline and at regular intervals. Subjective evaluations of hunger, energy, and appetite were also collected.	After 8 weeks, the Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract group lost an average of 3.79 lbs from baseline compared to loss of 1.65 lbs by the placebo group. The decrease in triglyceride levels from baseline was more than 3 times as high in the Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract group as in the placebo group (26.3 mg/dL vs. 8.2 mg/dL decrease). No adverse events considered by the authors to be related to treatment were reported. One subject in the placebo group reported abdominal pain, bloating, and gas. One subject in the Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract group complained of an increased incidence of tension headaches. No significant changes were noted in any of the other clinical parameters evaluated.

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**Table 5-5 Summary of clinical investigations of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (Cont'd)**

Reference	Number of Subjects Enrolled	Treatment	Duration	Parameters Measured	Results
Udani <i>et al.</i> , 2009	13 Adults (BMI of 18 and 25 kg/m <sup>2</sup> )	Subjects received 50 g net carbohydrates in the form of white bread with butter. Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract was administered at 1500 mg, 2000 mg, and 3000 mg, either in capsule or powder form. The powder form of the test product was mixed into the butter that was spread on the bread. The capsules were taken immediately prior to the ingestion of food.	Less than 2 weeks	Capillary blood was analyzed for blood glucose and was drawn twice at baseline and then at times 0 (start of meal), 15, 30, 45, 60, 90, and 120 minutes. Statistical analysis was performed by one-way analysis of variance (ANOVA) using unadjusted multiple comparisons (t tests) to the white bread control.	There was an apparent dose-related effect of Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract on the GI response to white bread with both powder and capsule formulations. For the capsule formulation, the 1500 mg dose had no effect on the GI and the 2000 mg and 3000 mg capsule doses caused insignificant reductions in GI. For the powder, the 1500 mg and 2000 mg doses caused insignificant reductions in the GI, and the 3000 mg dose had a significant effect. The authors reported that all of the dosages and formulations appeared to be well tolerated, and no adverse events were observed or reported during the study.

BMI: body mass index.

## 5.4 Clinical Studies of Dietary Supplement Products Containing Phase 2<sup>®</sup> White Kidney Bean (*Phaseolus vulgaris*)

Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is used as an ingredient in approximately 200 brands of nutritional supplement products marketed worldwide. Some of the dietary supplement manufacturers have shared the findings of their independent studies with Pharmachem. This information, summarized in Table 5-6 and described in more detail in subsequent sections, is included herein for completeness and as information corroborating the safety of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract.

Studies of various dietary supplements containing Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract were conducted in the United States and Europe. These were not safety studies *per se*. However, some of the studies measured blood glucose, cholesterol, triglycerides, liver function, kidney function, *etc.* Subjects in these studies received the supplements at levels providing 445 to 3000 g per day of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract with meals for periods from 30 days to 24 weeks. No adverse health effects were observed in any of these studies.

### 5.4.1 Study of the Effects of Blockal on the Body Composition of Overweight Men and Women

In a randomized, double-blind, placebo-controlled study, Cellano *et al.* (2007) investigated the body weight and body fat composition of generally healthy but overweight human volunteers before and after a 30-day oral treatment with a placebo (Batch 1600301) or a test dietary supplement (Batch D106B) preparation concurrently with a study diet. The test substance, Blockal, was in the form of an 800 mg tablet containing 445 mg of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (56% w/w), along with various other ingredients including 20% calcium phosphate, 10% microcrystalline cellulose, 7% Vitamin B3, and small quantities of other ingredients, including chromium picolinate (0.5 mg/800 mg tablet). The placebo contained primarily microcrystalline cellulose and maltodextrin (90% combined), and small amounts of milk thistle, cacao, and turmeric. Subjects were recruited through a market research company in Rome, Italy from a group of individuals that expressed a willingness to participate in such evaluations. The following selection criteria were used:

#### Inclusion criteria

- 5 to 15 kg overweight
- Consistently stable weight for at least 6 months
- Weight stability throughout a 30-day pretreatment period
- Good general health conditions
- No ongoing drug treatments
- Commitment to eating as prescribed by the nutritionist
- Commitment to avoiding the use of other weight loss products
- Commitment to avoid any changes in lifestyle throughout the test period (including sports and any activity that might affect test results)
- Non-participation in other similar tests during the 6 months prior to the study

### **Exclusion criteria**

- Pregnancy or breastfeeding
- Weight-reduction treatments during the 6 months prior to the study
- Any condition contrary to those indicated in the enrollment criteria

During a 30-day pre-treatment phase, subjects followed a study diet that provided approximately 2000 to 2200 calories per day, with the intake of complex carbohydrates concentrated in one of the two main meals (lunch or dinner). Body weights were measured at the beginning of this pre-treatment phase and after 10, 20, and 30 days. Only subjects that showed adequate body weight stability during this phase entered into the treatment phase, sixty overweight but otherwise healthy male and female volunteers between 20 and 45 years old. Subjects were equally divided to create two groups (placebo and test) comparable in age, gender, and body weight distribution.

During the treatment phase, subjects ingested one tablet per day of either the placebo or Blockal before the main carbohydrate-rich meal. Body weight, skin echogram, and waist, hip, and thigh circumference were measured at the beginning and end of the 30-day treatment phase. One subject in the placebo group withdrew from the study for unexplained reasons. No adverse events were reported.

At the end of 30 days, subjects consuming the Blockal supplement exhibited statistically significant reductions compared to placebo in average body weight (6.45 pounds vs. 0.76 pounds;  $p < 0.001$ ), fat body mass by bioelectric impedance (10.45% vs. 1.30%,  $p < 0.001$ ), skin adipose thickness by echography (11.63% vs. 1.30%,  $p < 0.001$ ), waistline circumference (3.44% vs. 0.53%,  $p < 0.001$ ), hip circumference (1.39% vs. 0.10%), and thigh circumference (1.44% vs. 0.39%,  $p < 0.001$ ). There were no reports of adverse side effects with the Blockal treatment or the placebo.

### **5.4.2 Study of Starch Away™ in Overweight Adults**

A study sponsored by Leiner Health Products examined the effects of Starch Away™, a supplement containing 500 mg Phase 2® white kidney bean (*Phaseolus vulgaris*) extract per soft chew on body weight loss among overweight adults. Sixty subjects received a placebo or 6 Starch Away™ soft chews per day, 2 before each meal [*i.e.*, 1000 mg Phase 2® white kidney bean (*Phaseolus vulgaris*) extract before each meal] for 12 weeks. Subjects were also educated on proper eating habits and the importance of exercise, but no specific diet or exercise regimen was prescribed.

Statistically significant body weight reduction was noted in the Starch Away™ group compared to placebo at Week 6 (-2.1 vs. 0 lbs,  $p=0.013$ ), Week 8 (-4.8 vs. -0.2 lbs,  $p=0.031$ ), and Week 12 (-6.9 vs. +0.8 lbs,  $p=0.029$ ). No adverse events were reported.

### 5.4.3 Study of Thera-Slim™ in Overweight and Obese Adults

A study conducted at the Capital Region Progressive Medicine and Longevity Practice, Albany, NY, examined the effects of Thera-Slim™ (manufactured by ProThera, Inc.), a supplement containing 500 mg of Phase 2® white kidney bean (*Phaseolus vulgaris*) extract and 250 mg fennel (*Foeniculum vulgare*) seed powder on body weight loss among overweight and obese adults. The placebo was a supplement containing cellulose and 250 mg of fennel seed powder (Erner and Meiss, 2004). The study design was a 24-week, placebo-controlled, double-blinded, randomized clinical trial with crossover of the placebo group at 12 weeks. The study population consisted of 50 male and female subjects, ages 18 to 70 years, with body mass indices (BMI) between 25 and 35, meeting the following eligibility criteria:

#### Inclusion Criteria

- Age >25 and <50 at time of screening
- BMI range 24-36
- Agree to continued treatment as directed
- Agree to periodic follow-up
- Agree to signed Consent Form

#### Exclusion Criteria

- Use of any of the following drugs within 4 weeks of screening
  - Meridia (sibutramine)
  - Xenical (orlistat)
  - Metabolife or any other ephedrine-containing product
  - Phenteramine
  - Diethylpropion
  - Phendimetrazine
  - Diuretics (except if already using to treat hypertension)
- Abnormal laboratory parameters (including at least one of the following):
  - Renal dysfunction (BUN >28 and serum creatinine >1.8)
  - Hepatic dysfunction (AST >57 M, 39 F; ALT >72 M, 52 F)
- Subjects unable to comprehend/follow the study protocol
- Active eating disorder, including bulimia, anorexia nervosa
- Known sensitivities to fennel seed or beans
- Significant depression or other psychiatric disease noted on the initial evaluation
- Active CAD, CHF, arrhythmia, or uncontrolled hypertension
- Severe hepatic or renal disease (except people with prior diagnosis of fatty liver even if LFTs are elevated)
- Pregnant or breastfeeding
- Seizure disorder
- History of cancer within last 5 years prior to evaluation (except basal or squamous cell cancer of skin)
- Anti-coagulation therapy
- Alcoholism
- Chronic malabsorption
- Inflammatory bowel disease (IBD)
- Diverticulosis/diverticulitis

Subjects were assigned to Group A or B and were instructed to continue their usual dietary intake, making sure to only consume starch-containing foods at any of 2 meals/day. The total amount of starch containing foods was to total anywhere between 100-200 g/day. With each starch-containing meal, subjects were told to take 2 capsules of A or B at the start of that meal. Subjects were further instructed not to consume starchy or "sweet" snacks between meals. They were told to maintain their typical levels of physical activity throughout the 24-week study period. Food record sheets were distributed at each visit and were to be brought in for review at

the next 4-week follow-up visit. At the end of each follow-up visit, subjects received a 4-week supply of capsule A or B.

At week 12, the study entered the crossover phase with associated un-blinding. Subjects receiving capsule A were informed by the investigator that they had been receiving a placebo capsule containing cellulose and 250 mg of fennel seed powder. Group B subjects were told that they were receiving Thera-Slim™ capsules, each capsule containing 500 mg of Phase 2® white kidney bean (*Phaseolus vulgaris*) extract and 250 mg fennel seed powder. The placebo and Thera-Slim™ capsules were identical in appearance and odor. Subjects then followed the same sequence of events as previously outlined. However, all participants were now aware they were taking active treatment. At week 24, half the subjects in this study had received Phase 2® white kidney bean (*Phaseolus vulgaris*) extract at 1000 mg/day for 24 weeks; the remainder received 1000 mg Phase 2® white kidney bean (*Phaseolus vulgaris*) extract per day for 12 weeks. Each participant underwent an exit visit, and all questions pertaining to their participation in the study were answered by the principal investigator.

All subjects underwent an initial comprehensive medical history and physical exam in conjunction with body composition analysis and lab assessment. Lab analyses were performed by Laboratory Corporation of America (Lab Corp). A brief behavioral assessment was performed to rule out eating disorders and depression. All subjects were in general good health with no active problems, except for a few cases of hyperlipidemia (unspecified) and mild, controlled hypertension. Several subjects had fasting insulin levels greater than 10  $\mu$ U/mL, but none had frank diabetes mellitus type 2.

A total of 60 subjects enrolled in the study. Six withdrew from the study, 3 each in groups A and B. The withdrawals were all related to inability to continue to fulfill the obligations of follow-up visits, lab work, etc. due to other commitments. At the study's conclusion, 27 participants remained in groups A and B with the ratio of female:male subjects being an identical 8.5:1 for each group. Demographically, groups A and B showed the average age of female participants to be 44 in group A and 41 in group B. The average age of male participants was 45 in both groups. The average BMI (body mass index) in groups A and B was 30 for female subjects. The average BMI for males was 31 in group A and 33 in group B. No dropouts occurred to side effects nor were there any adverse reactions or abnormal metabolic alterations during the study.

When data from all subjects in groups A (placebo-active) and B (active) were pooled, numerous observations were noted. Group A had an average weight gain of 1.5 lb per subject after 24 weeks. The weight gains during the placebo and cross-over periods were almost identical (0.6 vs. 0.87 lbs). Group B had an average weight loss of -1.1 lb per subject after 24 weeks. Weight loss was more notable for the first 12 weeks (-1.4 vs. -0.2 lbs) than during the second half of the study. Looking at median weight change, Group A had a median weight gain of two pounds vs. a median weight loss of one pound for Group B.

In Group A, 18 of 27 subjects gained weight during the placebo phase while 15 of 27 gained weight when switched to active treatment. By the end of the study, 16 of 27 had gained weight in Group A. In contrast 18 of 26 subjects in Group B (active for 24 weeks) lost weight during the first 12 weeks of treatment (1 subject had no change) and 15 of 27 subjects lost weight over the last 12 weeks of active treatment. Overall, 16 of 27 subjects lost weight during the 24-week study. In reviewing sequential waist and hip circumference measurements, both groups A and B showed minor decreases by study's end with reductions being slightly more prominent in Group B. Body fat changed less than 1% in both groups A and B showing slight elevations.

When reviewing lab parameters, both groups showed minor reductions in serum cholesterol levels (-10 Group A vs. -7 Group B). However, serum triglyceride levels dropped by almost 3.3-fold as much in Group B compared to Group A by study conclusion (-38.1 vs. -11.9). HDL levels remained essentially unchanged in both treatment groups while minor reductions in LDL were noted in both groups (-8.1 Group A vs. -5.2 Group B). Fasting insulin levels dropped by almost 2% in Groups A and B. Fasting glucose levels remained unchanged in Group A while dropping an average of 2 mg/dl in Group B by the study's conclusion.

One patient developed transient minimal increases in amylase and lipase levels during the 24-week study (amylase 121U/L [normal= 0-99]; lipase 126U/L [normal=0-59]). The subject had just returned from a cruise vacation during which time she drank alcohol somewhat frequently in contrast to her usual abstinence. She was otherwise asymptomatic. The values returned to normal 12 weeks later. Thera-Slim™ was judged to be modestly effective in reducing weight gain in group B, although non-compliance with study diet was considered problematic. However, no reports of adverse events from consumption of Thera-Slim™, providing 1000 mg of Phase 2® white kidney bean (*Phaseolus vulgaris*) extract per day, for either 12 or 24 weeks was reported by any study participant.

#### **5.4.4 Study of a Dietary Supplement Containing Phase 2® White Kidney Bean (*Phaseolus vulgaris*) Extract in Overweight Adults**

Using a randomized, double-blinded, placebo-controlled design, Wu *et al.* (2010) examined the effects of a dietary supplement containing Phase 2® white kidney bean (*Phaseolus vulgaris*) extract on the body weight of overweight men and women. Subjects (50 assigned to placebo group and 51 assigned to the supplement group) 20 to 50 years old, with a BMI between 25 and 40 participated in the study. Subjects received 2 capsules of either placebo or the dietary supplement 15 minutes before each meal for 60 consecutive days. The 2 test capsules provided a total of approximately 1000 mg of Phase 2® white kidney bean (*Phaseolus vulgaris*) extract; the total intake of the extract was 3000 mg per day. Body weights, waist and hip circumferences, and blood chemistry values were measured at the beginning, at 30 days, and at the end of the study. Subjects were monitored throughout the investigation for any adverse effects.

Compared to the placebo group, subjects receiving Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract had a statistically significantly greater average reduction of body weight and waist circumference. Also, corresponding with scale weight, compared to placebo, intake of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract was associated with a greater decrease in BMI at 30 days and at the end of the study. In general, blood chemistry values did not change markedly over the 2-month study period. There were no statistically significant differences between the placebo and treated groups, with 2 exceptions. Compared to subjects receiving the placebo, subjects receiving Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract had slightly higher mean creatinine levels and slightly lower mean GPT levels at the 30-day time point. No significant adverse events were reported.

**Table 5-6 Summary of clinical investigations of dietary supplements containing Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract**

Reference	Number of Subjects Enrolled	Treatment	Duration	Parameters Measured	Results
Cellano <i>et al.</i> , 2007	60 Overweight adults	After a 30-day run-in phase with a 2000 to 2200 calorie diet, subjects received Blockal batch 1600301 (placebo) or Blockal batch D106B [formulation containing 445 mg of Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract] once daily before consuming a carbohydrate-rich meal for 30 days.	60 days (30-day treatment)	Body weights and body fat composition were measured at the start and 10, 20, and 30 days after treatment.	The group given the formulation with Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract lost an average of 6.45 lbs in 30 days compared with an average of 0.766 lbs in the placebo group (p<0.001). Body fat composition was reduced by more than 10% in the Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract group compared with a 0.16% reduction in the placebo group. The results obtained at the end of the study showed that the test product had good tolerability characteristics.
Leiner Health Products, 2003 (Unpublished)  August, 2003	60 Overweight adults	Placebo or Starch Away™ soft chew supplement before each of 3 daily meals [total 3 g/day of Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract]. Subjects were also educated on proper eating habits and the importance of exercise, but no specific diet or exercise regimen was prescribed.	12 weeks	Body weights were measured at baseline and at Weeks 6, 8, and 12.	Statistically significant weight reduction noted in the Starch Away™ (Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract ) group compared to placebo at Week 6 (-2.1 vs. 0 lbs, p=0.013), Week 8 (-4.8 vs. -0.2 lbs, p=0.031), and Week 12 (-6.9 vs. +0.8 lbs, p=0.029). No adverse events were reported.
Erner and Meiss, 2004 (Unpublished)  Capital Region Progressive Medicine and Longevity Practice, Albany, NY, 2003	54 Overweight and obese adults (BMI of 25 to 35 kg/m <sup>2</sup> )	Subjects were randomly allocated to receive a placebo or Thera-Slim™, a supplement containing 500 g Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract and 0.5 g fennel seed powder, twice daily along with meals containing 100 to 200 g dietary starch for 12 weeks. After 12 weeks, all subjects received Thera-Slim™ in an open-label manner for another 12 weeks.	12 to 24 weeks	Body weights, body fat composition, blood cholesterol, triglycerides, HDL, LDL, fasting insulin, and fasting glucose were measured.	Only limited 12-week interim data were available. Study completion expected in early 2004. No side effects or adverse events were reported by any of the participants. There were no withdrawals from the study due to intolerance.

BMI: body mass index

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**Table 5-6 Summary of clinical investigations of dietary supplements containing Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (Cont'd)**

Reference	Number of Subjects Enrolled	Treatment	Duration	Parameters Measured	Results
Wu <i>et al.</i> , 2010	101 Volunteers with a BMI between 25-40 kg/m <sup>2</sup>	Placebo (2 capsules) or supplement (2 capsules) containing a total of 1000 mg of Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract administered 3 times daily 15 minutes before each meal.  50 subjects received placebo; 51 subjects received 3000 mg Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract per day.	60 days	Body weights, waist and hip measurements; blood chemistry values at baseline, 30 days, and end of study.	Compared to the placebo group, subjects receiving Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract had a statistically significantly greater average reduction of body weight and waist circumference.  Blood chemistry values did not change markedly. No statistically significant differences noted between placebo and treatment groups, except for: (1) higher creatinine levels in the treatment group at 30 days; and (2) lower mean GPT in the treatment group. These differences were not statistically significant at the end of the study.

BMI: body mass index; GPT: glutamate pyruvate transaminase.

## 5.5 Other Information Related to Safety

### 5.5.1 Case Report of Severe Anaphylaxis to Kidney Beans

Rouge *et al.* (2011) present a documented case report identifying phaseolin (vicilin) and phytohemagglutinin (PHA) lectin as putative allergens. Ingestion of cooked kidney beans by a 23-year old female having no atopic history caused a systemic reaction up to an anaphylactic shock 30 minutes after consumption of the beans. She required epinephrine and steroid treatment. The patient further experienced less severe systemic reactions related to previous kidney bean ingestion. Skin prick test with crushed cooked kidney bean resulted in a wheal of 15 mm associated to pseudopodes with an erythema of 25 mm. Skin prick tests for other related food (peanut, soybean) were all negative.

The kidney bean allergen(s) was identified from a protein extract prepared from crude or previously boiled kidney beans crushed in 20 mM Tris-buffered saline. Upon transfer of the protein fractions to a nitrocellulose membrane, a Western blot performed in the presence of 1:10 diluted patient serum revealed 5 main IgE-reacting protein fractions. A trypsin digestion of the IgE-reactive fractions, followed by mass mapping, unambiguously identified phaseolin and PHA as the putative allergens. Both phaseolin and PHA consist of oligomeric proteins resistant to heat denaturation and digestive proteolysis, exhibiting an extended surface susceptible to display IgE-binding epitopic regions that most probably account for their allergenic propensity. The authors concluded that in addition to cupin allergens, lectins thus appear as potentially allergenic proteins of edible legume seeds.

Despite being related to one of the most common food allergens (*i.e.*, peanuts), kidney beans are not known to be potent allergens, although they can produce toxicity when consumed raw or undercooked (see section 5.5.2 below). Nevertheless, allergies to many foods that are not common allergens can develop sporadically in a small subset of the population.

### 5.5.2 Anti-Nutritive Substances Naturally Present in Beans

Raw *Phaseolus vulgaris* beans are reported to naturally contain a variety of anti-nutritional and potentially toxic substances, such as phytohemagglutinins (PHA), which are lectins found in plants, especially legumes, and trypsin inhibitors. PHA cause agglutination of mammalian red blood cells; trypsin inhibitors interfere with the digestive enzyme trypsin.

Ingestion of raw or improperly prepared kidney (*P. vulgaris*) beans has been associated with reduced feed efficiency, impaired weight gain, histopathological changes, and occasional deaths in livestock and laboratory animals. In humans, consumption of raw or undercooked kidney beans has been associated with severe but transient gastrointestinal disturbances (Haidvogel *et al.*, 1979; Rodhouse *et al.*, 1990; Sockett *et al.*, 1993). These effects have been attributed largely to PHA.

Depending upon natural variation, the red kidney (*P. vulgaris*) bean is known to contain up to five tetrameric isolectins: L<sub>4</sub>, L<sub>3</sub>E<sub>1</sub>, L<sub>2</sub>E<sub>2</sub>, L<sub>1</sub>E<sub>3</sub>, and E<sub>4</sub> (Green and Baenziger, 1987). Lectins constitute a class of carbohydrate-binding glycoproteins found in both plants and animals. Varying proportions of leukocyte reactive (L-PHA) and erythrocyte reactive (E-PHA) polypeptide subunits may be present at high levels in raw kidney beans but are reduced by cooking. For example, raw kidney beans may contain 20,000 to 70,000 hemagglutinating units (HU)<sup>4</sup> per gram compared to 200 to 400 HU per gram in cooked beans. There is also some variation among bean types in PHA concentrations. Colored beans, particularly large-seeded kidney beans, have high levels of PHA, whereas small white navy beans are reported to have negligible levels of these lectins (Uebersax, 2001). Red kidney beans have about 3 times the amount of PHA present in white kidney beans (U.S. FDA/CFSAN, 1992).

As previously mentioned, production lots of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract are regularly tested *in vitro* for hemagglutinating and trypsin inhibition activities. Data from assays of several lots of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (see Table 3-4) show very low levels of hemagglutinin activity (HA) and trypsin-inhibiting activity (as trypsin inhibitor units or TIU)<sup>5</sup>. The HA of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract ranged from 20 to 641 HU per g of sample (22 to 681 HU/g sample on a dry weight basis), compared to 32,000 HU/g for soybean lectin. The trypsin-inhibiting activity of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract ranged from 14.32 to 18.82 TIU (trypsin inhibitor units) per mg of sample, compared to 60.71 TIU/mg sample (68.76 TIU/mg sample on a dry weight basis) for defatted soybean flour.

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<sup>4</sup> A hemagglutinin unit (HU) is defined as the least amount of hemagglutinin that produces positive evidence of agglutination.

<sup>5</sup> TIU = trypsin inhibitor units (based on absorbance at 410 nm).

## 6.0 SUMMARY

Pharmachem Laboratories, Inc., with the assistance of a panel of experts (*i.e.*, individuals qualified by scientific training and experience who are specifically convened for this purpose), wishes to make a determination that the use of a dried aqueous extract derived from the common white kidney bean (*Phaseolus vulgaris*) marketed primarily under the name Phase 2<sup>®</sup> in foods is generally recognized as safe (GRAS) based on scientific procedures. In the United States, GRAS substances added to food are exempt from the definition of “food additive” and thus from the premarket approval requirements outlined in section 201(s) of the Federal Food, Drug, and Cosmetic Act. A determination that a substance is GRAS requires both technical evidence of safety and a basis to conclude that this technical evidence of safety is generally known and accepted.

Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is a dried aqueous extract manufactured under good manufacturing practices (GMP) to meet established composition and quality standards. It is intended to be used in foods as a substance offering nutritive value, based on its ability to inhibit the activity of the digestive enzyme  $\alpha$ -amylase *in vitro*, and the potential to interfere with carbohydrate digestion. It would be incorporated into foods for the general population at levels providing an aggregate intake of up to 10 grams per person per day (10 g/person/day).

Table 6-1 lists the levels of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract administered to rats in various oral (gavage) toxicity studies. No mortality or signs of toxicity were noted following administration of a single dose of the extract at up to 5000 mg/kg bw or multiple doses up to 2500 mg/kg bw/day for 28 days or up to 1112 mg/kg bw/day for 90 days. Also shown in Table 6-1 is what these dosages would be equivalent to in a human weighing 70 kg. The doses administered to rats as a single dose, over 28 days, and over 90 days, would be equivalent to 350, 175, and 77.8 g/day, respectively. Compared to the proposed aggregate intake of 10 g/person/day, the levels of exposure in rats were 7 to 35 times higher. Although an uncertainty factor of 100 is generally applied (10 each to account for interspecies and intraspecies variability) when extrapolating from rodent data to humans, in the present case, a margin of safety of 7 to 35 times below the exposures in rats (that induced no toxicity) is considered appropriate for the following reasons:

- Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is derived from the common white kidney bean, which has a long-time presence in the human diet. Raw or undercooked kidney beans naturally contain the anti-nutritive substances such as hemagglutinins (lectins) and trypsin inhibitors, which have been associated with adverse effects in humans and other animals. These would be the substance of greatest toxicological concern. However, routine tests of production lots show that these

substances are present at very low levels in Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract;

- The enzymatic effects are comparable across species, reducing the uncertainty regarding interspecies variability;
- The results of multiple clinical investigations in which hundreds of healthy subjects receiving Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract (as is or as an ingredient in dietary supplements) at levels ranging from 500 to 3000 mg/day for periods from 30 days to 24 weeks showed no treatment-related adverse effects. While the primary objective of these studies was to assess the effects on glucose response and body weight loss, a subset of the studies included some measures of safety, such as hematology, clinical chemistry, and/or urinalysis; and
- Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract is currently used in various forms (e.g., tablets, capsules, chewables, powdered drinks, chewing gums, baking mixes) in products marketed worldwide under approximately 200 brand names. These products provide up to 4500 mg/day (4.5 g/day) Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. To date, Pharmachem Laboratories, Inc. has had no reports of adverse events despite cumulative sale of 500,000 kg Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract.

**Table 6-1 Summary of nonclinical safety studies of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract and corresponding human exposure**

Test substance	Source	Highest dose of Phase 2 <sup>®</sup> extract tested with no adverse effect	Uncertainty factor applied	Corresponding human exposure <sup>1</sup>	
				Total	Compared to the proposed intake of 10 g/day
Phase 2 <sup>®</sup> white kidney bean ( <i>Phaseolus vulgaris</i> ) extract	Rat acute (single-dose) oral toxicity study	5000 mg/kg bw	none	350 g	35 times greater
	Rat 28-day oral toxicity study	2500 mg/kg bw/day	none	175 g/day	17.5 times greater
	Rat 90-day oral toxicity study	1000 mg/kg bw/day	none	70 g/day	7 times greater
Blockal dietary supplement	Rat acute (single-dose) oral toxicity study	1668 mg/kg bw/day	none	116.8 g/day	11.7 times greater
	Rat 90-day oral toxicity study	1112 mg/kg bw/day	none	77.8 g/day	7.8 times greater

<sup>1</sup> Based on an assumed human body weight of 70 kg.

The present document summarizes the available information supporting the safety of Phase 2<sup>®</sup> white kidney bean (*Phaseolus vulgaris*) extract. This information is intended to support a conclusion that there is consensus among qualified experts that there is reasonable certainty

that the substance is not harmful under the intended conditions of use and is therefore GRAS. The intended conditions of use are as an ingredient added to foods for its nutritive value with an intake not exceeding 10 grams per person per day.

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SUBMISSION END

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