'SCIENTIFIC RATIONALE' DOCUMENT

Partially Hydrolyzed Guar Gum (PHGG) Fiber

In order to facilitate the preparation of the 'scientific rationale' document and ensure that all required information is included, the following template may be conveniently used.

1. Food or food constituent considered to be responsible of the claimed effect

Partially Hydrolyzed Guar Gum (PHGG) Fiber

2. Targeted health benefit, and appropriate endpoints

The health benefit relates to PHGG fiber's role in supporting digestive health.

Digestive health is assessed by measuring bowel functioning and intestinal comfort as follows:

- Improvement of bowel functioning: bowel movement frequency, stool consistency, stool outputs, satisfaction of subjects with their bowel habits
- Reduction of intestinal symptoms: mainly self-rated questionnaires on global intestinal symptom scores and individual symptoms scores including abdominal pain/discomfort/cramping, abdominal bloating, flatulence which are associated with GI discomfort.

3. Proposed health claim wording

"PHGG fiber contributes to support digestive health" can be considered as a general claim and the specific claims are:

Master wordings:

1) PHGG fiber contributes to normal bowel movement.

2) PHGG fiber contributes to digestive comfort.

Different Nestlé Health Science products under the brands SUSTAGEN, PRONOURISH, BOOST, NUTRISOURCE, RESOURCE, MERITENE and OPTIFIBRE will bear the function claims pertaining to PHGG fiber.

4. Type of food/food matrix where the food or food constituent is to be added

PHGG fiber is added in food products (e.g. milk products, dairy-based drinks, nutritional drinks) with other fibers, probiotics or vitamins and minerals, in powder for reconstitution with water and ready-to-drink formats.

It is also used as Dietary or Food Supplement on its own in powder form.

5. Conditions of use

a. Total amount known to exert the effect

To bear the function claims for PHGG fiber, the products need to provide minimum of 5 g PHGG fiber per day as the total amount known to exert the claimed effect on bowel movement and digestive comfort.

b. Minimum amount per serving

The products shall meet the minimum PHGG requirement to bear the function claims. PHGG fiber shall be contained in 1 or several servings of the product per day to provide minimum of 5 g per day as total.

Examples:

RESOURCE Fiber Supplement: 2.58 g PHGG fiber per serving
BOOST Drink with PHGG: 7 g PHGG fiber per serving

c. Recommended consumption pattern

The recommended number of serving(s) depend on each product formulation. 1 or several servings is sufficient to obtain the total amount of 5 g PHGG fiber per day.

d. Additional mandatory statements (e.g. vulnerable groups)

Not applicable

e. Maximum safe intake

Several expert panels have concluded that PHGG is safe at doses of 20 g/d or higher. Its safety and efficacy have been tested in different populations (healthy adults, elderly, critically ill patients) and products containing PHGG have been in the market for over 2 decades with no adverse effects reported. PHGG has been used by Nestlé as a powdered supplement (classified as an FSMP, medical food, or dietary supplement, depending on the market), and as a source of fiber in liquid enteral nutrition products, at doses of 5 to >20 g/d without negative effects. (Klosterbuer, Abigail. “R&D NOTE”. Nestlé R&D Center Minneapolis. 7 November 2014)

6. Targeted population group

For children 4 years old to adults

7. Written summary of the scientific evidence

• The totality of the clinical scientific evidence obtained in the relevant target population and investigating digestive health benefits (improvement of intestinal symptoms and bowel functioning) has been considered.

• PHGG is sufficiently characterized (EFSA Journal 2011;9(6):2254).

• The measures (i.e. reduction of GI discomfort and maintenance of normal defecation) related to the claimed effect (digestive health) is well defined and considered beneficial for the targeted population (EFSA Journal 2016;14(1):4369, see section 8.b).

• A cause and effect relationship between consumption of PHGG and a benefit on digestive health relies on a significant number of clinical studies (19) among which 18 showed positive results (see section 9).

- Main clinical evidence (randomized, double blind, controlled studies): 3 positive clinical studies; 1 pilot studies (n=11) negative for transit time outcome).

- Supportive clinical evidence (Open trials): 15 positive clinical studies

• The scientific evidence was obtained in study groups representative of our target population: In healthy adults; IBS subjects for which extrapolation to the healthy population has been recognized by EFSA; “constipated” Japanese subjects using Japanese criteria of constipation which do allow inclusion of subjects not considered constipated in EU (see section 8.e); Children with IBS symptoms or constipation.

• The documented effective dose of as low as 5g per day of the fiber PHGG shall be achieved by consumption of SUSTAGEN, PRONOURISH, BOOST, NUTRISOURCE, RESOURCE, MERITENE and OPTIFIBRE products following the respective recommended number of servings per day.

• 5 g dietary fibers per day provide up to 20% of the DRV for dietary fiber known to have a sub-optimal intake in a large part of the population which should, therefore, be in favor of supporting digestive health (see section 9).

• The scientific evidence, with 3 out of 4 randomized, double blind, controlled studies being positive for digestive health related outcomes (see section 9) and 15 positive open trials, show aligned support behind PHGG fiber to support digestive health.

A cause and effect relationship is well established between the consumption of PHGG at the proposed dose and the claimed effects (bowel function and intestinal/digestive comfort).

8. Detailed description of the scientific evidence

a. Characterization of ingredient

PHGG is supplied by Taiyo under the trade name of Sunfiber®. The composition, physico-chemical characteristics and manufacturing process is well characterized (see Tayio dossier (Sunfiber® PHGG Dossier) and (Seon-Joo Yoon et al., 2008) for more details). This ingredient is also considered to be sufficiently characterized by EFSA (PHGG EFSA Journal 2011).

As a summary, the guar plant (Cyamopsis tetragonolobus) and guar seed from which PHGG originates are cultivated in India and Pakistan. PHGG is produced with a controlled partial enzymatic hydrolysis of guar gum seeds, during which Galactomannans are partially hydrolysed by endo-ß-D-mannanase extracted from Aspergillum niger and then purified. The major polysaccharide of PHGG is Galactomannan. PHGG structural formula is β-D-(1-4)-linked manno-pyranose-units - mannose:galactose ratio = ~ 38:62 and its average molecular weight of about 20,000 Daltons.

PHGG is a natural, water soluble, highly fermentable dietary fiber primarily used for a nutritional purpose, i.e. for fiber-enrichment of process foods. Sunfiber® contains more than 76% fiber (AOAC Method).

PHGG is a dietary fiber as defined by Codex definition (CAC/GL 2-1985) that states that “Dietary fibre means carbohydrate polymers[1] with ten or more monomeric units[2], which are not hydrolysed by the endogenous enzymes in the small intestine of humans and belong to the following categories:
• Edible carbohydrate polymers naturally occurring in the food as consumed,
• Carbohydrate polymers, which have been obtained from food raw material by physical, enzymatic or chemical means and which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities,
• Synthetic carbohydrate polymers which have been shown to have a physiological effect of benefit to health as demonstrated by generally accepted scientific evidence to competent authorities.”

(1) When derived from a plant origin, dietary fibre may include fractions of lignin and/or other compounds associated with polysaccharides in the plant cell walls. These compounds also may be measured by certain analytical method(s) for dietary fibre. However, such compounds are not included in the definition of dietary fibre if extracted and re-introduced into a food.
(2) Decision on whether to include carbohydrates from 3 to 9 monomeric units should be left to national authorities.

PHGG is a dietary fiber because it is not a fermentable substance and has physiological benefits as below:
• Improved bowel movement regularity
• Reduced bloating, flatulence, abdominal cramps

US FDA published last May 2016 new definition for ‘Dietary Fiber’.

“Dietary fiber is defined as non-digestible soluble and insoluble carbohydrates (with 3 or more monomeric units), and lignin that are intrinsic and intact in plants; isolated or synthetic non-digestible carbohydrates (with 3 or more monomeric units) determined by FDA to have physiological effects that are beneficial to human health.” The only non-digestible carbohydrates that were then regarded by US FDA to conform to the new definition, therefore, qualified as fiber are beta-glucan soluble fiber, psyllium husk, cellulose, guar gum, pectin, locust bean gum, and hydroxypropylmethylcellulose.
Last August 19, 2016, US FDA Department of Health & Human Services confirms that partially hydrolyzed guar gum (PHGG) meets its definition of a dietary fiber, supported by sufficient scientific evidence and is included in their dietary fiber definition for guar gum.

In Japan, PHGG is regarded as a functional food ingredient. Functional food ingredients have to be recognized by a government-owned agency responsible for publishing a monograph for food ingredients before being permitted for use. The monograph which details the review of the safety, physiological effects and functionality of PHGG was first published in March 1990. Thus, no pre-approval is required now for PHGG in the country. In the US, PHGG was granted a Generally Recognized As Safe (GRAS) status by the FDA. In Europe, the Belgian High Council of Health first approved PHGG in 1992. In 1993, the Ministry of Health approved its use in solid foods and was further extended for use in liquid foods in 1996. The Spanish Ministry of Health also accepted the use of PHGG in functional foods and supplements. Dutch Food Authority also accepted its use in both solid and liquid foods. The Swiss Federal Office of the Public Health also approved the use of PHGG in 1992. In 1997, European

Union Novel Foods Regulation committee approved PHGG for food applications throughout all the EU countries. (Cho and Samuel, 2009)

b. The claimed effect is beneficial to human health

Physiological benefits related to digestive health, also referred as gut health, includes the reduction of gastrointestinal discomfort (symptoms) and the maintenance of normal bowel functioning / defecation (EFSA Journal 2016;14(1):4369). EFSA stated that both are beneficial to human health.

Beyond any functional benefit, dietary fiber is an important component of a healthy diet, in particular to support intestinal health (Rose et al., 2010). A daily intake of 25 g of dietary fiber is set as a Dietary Reference Value (DRV) because it is adequate for normal bowel function in adults (EFSA panel, 2010).

Consumption of SUSTAGEN, PRONOURISH, BOOST, NUTRISOURCE, RESOURCE, MERITENE and OPTIFIBRE products following the respective recommended number of servings per day would provide the amount of PHGG fiber, which constitutes a significant support toward ingestion of a healthy diet.

c. An association (cause and effect relationship) is established between the consumption of the food or food constituent and the claimed effect in humans

A cause and effect relationship between consumption of PHGG and a benefit on digestive health relies on a significant number of clinical studies (19) among which 18 showed positive results (see section 9).

3 positive randomized, double blind, controlled studies out of 4, together with 15 positive supportive open trials show aligned support behind PHGG fiber to support digestive health.

A cause and effect relationship is well established between the consumption of PHGG fiber at the proposed dose and the claimed effects (bowel function and intestinal/digestive comfort).

d. The quantity of the food or food constituent and frequency of consumption required to obtain the claimed effect can reasonably be achieved as part of a balanced diet

PHGG fiber shall be contained in 1 or several servings of the product per day to provide minimum of 5 g per day as total. Recommended number of servings depend on each product formulation. 1 or several servings is sufficient to obtain the total amount of 5 g PHGG fiber per day.

• 5 g dietary fibers per day provide up to 20% of the DRV for dietary fiber known to have a sub-optimal intake in a large part of the population which should, therefore, be in favor of supporting digestive health (see section 9).

e. The specific study population in which the evidence was obtained is representative of the target population

The scientific evidence related to intestinal comfort has been mainly substantiated in IBS subjects. It can be used for a claim on gastrointestinal comfort targeted at the general population as stated by EFSA (EFSA Journal 2016;14(1):4369).

The scientific evidence related to bowel functioning was substantiated in healthy subjects, subjects with bowel movement irregularity (constipation, mild constipation) and IBS subjects exhibiting all syndrome subtypes (IBS-Diarrhea, IBS-Constipation, IBS-Mixed predominance).

The studies targeting an improvement of bowel movements in “constipated” Japanese subjects considers ≤ 4 bowel movements per week as indicator of constipation which defers from the European and US definition of constipation (< 3 bowel movements per week) (example: Takahashi et al., 1994). Therefore Japanese studies performed on “constipated” subjects were considered in this dossier, being more representative of the healthy population with a low regularity of bowel movements per week.

9. Tabulated summary of pertinent studies

Since the negative opinion from EFSA in 2011 on some health claims related to PHGG, there are new clinical data which show beneficial effects of PHGG on digestive health.

Digestive health as measured by improvement of intestinal comfort (intestinal tolerance and reduction of intestinal symptoms)

9 clinical studies investigated the benefit of PHGG for supporting intestinal comfort.

Main clinical evidence: Randomized, double-blind, controlled, parallel or cross-over studies

The scientific clinical evidence is detailed in table 1.

3 clinical studies have tested the beneficial effect of PHGG to improve intestinal symptoms in IBS subjects (1 study in children).

• Parisi et al (2002) showed that a greater proportion of IBS subjects reported overall treatment satisfaction (60% IBS, global estimate of abdominal pain and bowel habits) when receiving PHGG (5 g/d) rather than wheat bran (40% IBS). More subjects switched from wheat bran to PHGG (50% of them) than from PHGG to wheat bran (11%) at 4 wks of treatment, for treatment satisfaction reasons (global estimate of abdominal pain and bowel habits).

• Romano et al (2013) showed significant improvement of IBS symptoms in children receiving 5g/d PHGG in fruit juice for 4 wks, vs placebo (fruit juice).

• Niv et al (2016) showed a significantly greater improvement of bloating and bloating plus gas scores in IBS subjects receiving PHGG (3g/d as starting dose for adaptation, then up to 6 g/d) compared to placebo (maltodextrin 3 to 6 g/d).

Supportive clinical evidence: Open trials *vs.* baseline, or cross-sectional studies

The scientific clinical evidence is detailed in table 1.

6 clinical studies have tested the beneficial effect of PHGG to improve intestinal symptoms in IBS subjects, *vs*. baseline (including 2 studies in children).

• Giaccari et al (2001) showed reduction of bloating, flatulence and abdominal cramping from wk 3 in IBS subjects supplemented with 5 g/d PHGG *vs*. baseline.

• Parisi et al (2005) showed a significant improvement of gastrointestinal symptoms and QOL in IBS subjects receiving PHGG (5 to 10 g/d) *vs*. baseline. The beneficial effect, observed from 4 wks of treatment till end of the study (12 wks) was still significant at 6 months follow-up, but to decreased extent compared to the end of PHGG treatment.

• Ustundag et al. (2010) showed that 3g/day (4-6 yo) to 5g/day (12-16 yo children) PHGG for 4 wks in children with constipation significantly decreased abdominal pain *vs*. baseline, as effectively as the positive lactulose control group (osmotic laxative).

• Prasad et al (2011) showed improvement of abdominal pain vs. baseline in 68% children with IBS symptoms (13 out of 29)) after 6 to 8 wks of treatment (PHGG dose not indicated).

• Polymeros et al (2014) showed a significant decrease in abdominal pain (secondary outcome) in IBS–C subjects taking 5 g/d PHGG *vs*. baseline, for which a significant improvement of colonic transit time (primary outcome) was also observed.

• Russo et al (2015) showed a significant reduction of global intestinal symptoms in IBS subjects consuming PHGG (dose unknown) *vs*. baseline.

Digestive health as measured by improvement of bowel functioning (bowel movement regularity, consistency, stool output, intestinal transit, bowel habit self-rated satisfaction, reduced need for laxatives)

13 clinical studies investigated the benefit of PHGG for improving bowel functioning.

Main clinical evidence: Randomized, single-blind or double-blind, controlled, parallel or cross-over studies

The scientific clinical evidence is detailed in table 1.

2 clinical study tested the beneficial effect of PHGG to improve bowel functioning (1 study in children).

• Lampe et al (1992) showed, in healthy men, no significant effect of PHGG supplementation (15g/d for 18 days) on transit time vs a CTRL supplementation (0 g/d fiber), and lead to a longer transit time and lower fecal moisture content vs soy polysaccharide (15 g/d) or a self-selected diet. PHGG supplementation did not significantly

improve daily fecal output and frequency of defecation when compared to the CTRL or soy polysaccharide supplementation.

• Romano et al (2013) showed significant improvement of bowel habits (constipation, diarrhea) in IBS children receiving 5g/d PHGG in fruit juice for 4 wks (40% improved) vs those receiving placebo (fruit juice, 13.3% improved)

Supportive clinical evidence: Open trials *vs.* baseline, or cross-sectional studies

The scientific clinical evidence is detailed in table 1.

11 clinical studies have tested the beneficial effect of PHGG to improve bowel functioning, mainly in healthy adults, in IBS children with altered bowel movements (1 study), in constipated children (1 study) and in adults defined as constipated with Japanese criteria, *vs*. baseline. 1 clinical study has tested the benefit of PHGG to counteract FODMAP (polyols)-induced intestinal intolerance (diarrhea).

• Takahashi et al (1993) showed that 36 g PHGG/d for 4 wks significantly increased fecal weight and output frequency in healthy men, vs. control and free diet periods.

• Takahashi et al (1994) showed that 11g PHGG/d for 3 wks increased defecation frequency and fecal moisture in constipated women (≤ 4 bowel movements per wk), *vs*. baseline control periods (regular diet).

• Yamatoya et al (1995) showed that both 5g/ PHGG and 15 g/d PHGG significantly increased defecation frequency and the recall fecal volume *vs*. baseline control periods in healthy volunteers without constipation.

• Patrick et al (1998) showed that a gradual increased supplementation of 4 to 12 g PHGG/d over a week in nursing home ageing subjects receiving 50% of their usual laxative daily dose significantly reduced further the laxative intake vs baseline (twice more laxative dose without PHGG), and provided satisfaction to subject's *vs*. previous use of laxative alone.

• Okazaki et al (1999) showed that 10g/d PHGG increased the number of defecation per week *vs*. baseline control period (same beverage without PHGG in healthy volunteers. 5g/d PHGG also increased the number of defecation *vs*. a control period 1 wk before starting PHGG consumption.

• Tanaka et al (2000) showed that rice gruel containing PHGG (7 g/d) increased the number of defecation per wk and the fecal volume *vs*. placebo (0g fiber) controlled baseline period, in healthy women exhibiting or not constipation as defined by Japanese criteria (≤ 4 bowel movements per wk).

• Sakata et al (2006) showed, in healthy volunteers, that 12.5 g/d PHGG for 14 days significantly modified fecal bulk toward an increase in 4 subjects out of 9 or decrease in 2 subjects out of 9, and lead to softened (3 subjects) or harder (4 subjects) stools *vs*. baseline dietary controlled period. The fecal moisture was increased in 5 subjects and decreased in 2 subjects.

• Nakamura et al (2007) showed that the diarrhea event owing to maltitol ingestion was significantly improved by 5 g PHGG in 10 of 28 healthy volunteers, and strongly suppressed by 10 g PHGG. The diarrhea event owing to lactitol was improved by 5 g PHGG in 7 of 19 volunteers.

• Ustundag et al. (2010) showed that 3g/day (4-6 yo) to 5g/day (12-16 yo children) PHGG for 4 wks in children with constipation significantly increased bowel movement frequency and consistency and decreased rectal bleeding *vs*. baseline as effectively as the positive lactulose control group (osmotic laxative).

• Prasad et al (2011) showed improvement of alternating diarrhea and constipation in 82% of children with IBS symptoms (23 out of 28) and improvement of diarrhea in 58% of children (11 out of 18), vs. baseline after 6 to 8 wks of treatment (PHGG dose not indicated).

• Maeda et al (2012) showed that 10 g/d PHGG supplemented to patients on maintenance dialysis who are experiencing constipation as defined by Japanese criteria (≤ 4 bowel movements per wk), significantly decreased constipation scores assessed by a Japanese scale *vs*. baseline (no supplementation),.

Additional clinical studies assessing the benefit of PHGG to improve diarrhea have been performed in "non-healthy" target populations. They are not described into the details in this dossier since less scientifically relevant to the population targeted by products refered in this dossier. As they strongly support the role of PHGG for digestive health benefits, a high level summary of the substantiation is provided below as supportive evidence.

6 Randomized, double blind, controlled trials showed:

- Reduction in diarrhea incidence / days with diarrhea in post-operative patients receiving total enteral nutrition or enteral nutrition (20g PHGG/L; Homann et al 1994); Patients with severe sepsis and septic shock, receiving 22g/L PHGG in enteral formula (Spapen et al., 2001); ICU patients with pre-existing diarrhea receiving enteral feeding with 2% PHGG (Rushdi et al 2004); Patients receiving total enteral nutrition following upper gastrointestinal surgery, receiving 20g PHGG/d (Homanna, et al 2004)

- Reduction in duration of diarrhea in 150 children aged 4 to 18 months who had watery diarrhea, when PHGG is combined with an oral rehydration supplement (20g/L, Alam et al., 2000)

- Treatment of diarrhea in 116 children aged 5–24 months with persistent diarrhea (20g/L PHGG, Alam et al 2005).

1 Open trial showed:

- Reduction of the water content of the feces and frequency of daily bowel movements in 20 elderly subjects (80 yo) who had diarrhea during long-term nutrition management (up to 28g PHGG/d, Nakao et al 2002)

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11. Safety Considerations

Partially Hydrolyzed Guar Gum has been used for many years with no adverse effects reported. In the US, powdered PHGG supplement (originally branded Benefiber; now Nutrisource Fiber) has been in the market since 1992 (originally by Sandoz, then Novartis, and now Nestlé). The product is available as a dietary supplement, but was also classified in the past as a medical food. The maximum recommended dosage depends on the doctor's discretion. It is recommended to start with 1 serving/d and to gradually increase the dose to meet recommendations for total fiber intake (25 g/d). No safety concerns have been reported from the use of this product. In Europe, powdered PHGG supplement has been marketed by Nestlé as an FSMP under the name OptiFibre in Europe since 2009. Recommended daily dosage is 5-25 g Optifibre per day or according to doctor's recommendations. It is advised to increase the dosage gradually. No safety concerns have been reported from the use of this product. In addition, Benefiber (Novartis) in Switzerland, a powdered PHGG supplement, is available in pharmacies and drugstores. The maximum daily amount recommended for adults and adolescents 12 years and older is 40 g/d (32 g soluble fiber). (Klosterbuer, Abigail. "R&D NOTE". Nestlé R&D Center Minneapolis. 7 November 2014)

Many clinical studies have been performed with PHGG, showing safety and good tolerance.

In the Report of the Scientific Committee of the Spanish Agency for Food Safety and Nutrition (AESAN) on the use conditions for certain substances other than vitamins, minerals and plants in food supplements, it was said that several toxicological studies were done on rats and humans and tolerance turned out to be good, food intake, body weight and biochemical markers were not affected nor were there signs of adverse effects that may be attributed to the substance.

A randomized, double-blind, crossover trial showed that PHGG did not interfere with absorption of glucose, amino acids, or fat, and had no adverse effects on hematological, hepatic, pancreatic, or renal function in subjects consuming liquid diets containing 21 g/L PHGG. In addition, consumption of 36 g/d PHGG for 4 weeks did not inhibit intestinal absorption of calcium, iron, or zinc in healthy men consuming a controlled diet (basal diet provided an additional 21 g/d dietary fiber). Healthy volunteers consuming liquid diets with 21 g/L PHGG (average intake of 42 g fiber/d) for 7 days did not report gastrointestinal symptoms or diarrhea.

In Japan, functional food ingredients have to be recognized by a government-owned agency responsible for publishing a monograph for food ingredients before being permitted for use. The monograph which details the review of the safety, physiological effects and functionality of PHGG was first published in March 1990. Thus, no pre-approval is required now for PHGG in the country. In the US, PHGG was granted a Generally Recognized As Safe (GRAS) status by the FDA. In Europe, the Belgian High Council of Health first approved PHGG in 1992. In 1993, the Ministry of Health approved its use in solid foods and was further extended for use in liquid foods in 1996. The Spanish Ministry of Health also accepted the use of PHGG in functional foods and supplements. Dutch Food Authority also accepted its use in both solid and liquid foods. The Swiss Federal Office of the Public Health also approved the use of PHGG in 1992. In 1997, European Union Novel Foods Regulation committee approved PHGG for food applications throughout all the EU countries. (Cho and Samuel, 2009)

References:

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