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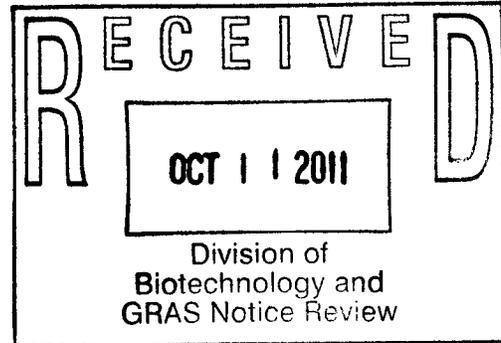
ORIGINAL SUBMISSION

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October 7, 2011



Dr. Antonia Mattia, 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

RE: PolyGlycopleX® (PGX®) GRAS Notification

Dear Dr. Mattia:

In accordance with proposed 21 CFR §170.36 (a notice of a claim for exemption based on a GRAS determination), published in the Federal Register (62 FR 18937-18964), I am submitting in triplicate, as the agent of the notifier, Inovo Biologic Inc., 104 – 1240 Kensington Rd. NW, Suite 409, Calgary, Alberta Y2N4Y7, Canada, a notification of GRAS status for the use of PolyGlycopleX® (PGX®) soluble polysaccharide complex as a source of fiber in the diet and/or as a thickener or stabilizer in foods, at a maximum consumption level of 10,070 mg/day. A GRAS expert panel dossier, setting forth the basis for the GRAS determination, as well as *curriculum vitae* of the members of the GRAS panel, are included by reference.

Best regards,

(b) (6)



Ray A. Matulka, Ph.D.

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1. GRAS Exemption Claim

A. Claim of Exemption from the Requirement for Premarket Approval Pursuant to Proposed 21 CFR 170.36(c)(1)

PolyGlycopleX[®] (PGX[®]) soluble polysaccharide complex has been determined by Inovo Biologic Inc., on the basis of advice from its Expert Panel, to be generally recognized as safe (GRAS) and therefore, exempt from the requirement of premarket approval, under the conditions of its intended use as described below. The basis for this finding is described in the following sections.

Signed,

(b) (6)



Date October 7, 2011

Ray A. Matulka, Ph.D.
Burdock Group
801 N. Orange Avenue Suite 710
Orlando, FL 32801

(i) Name and Address of the Notifier

Inovo Biologic Inc.
104 - 1240 Kensington Rd. NW, Suite 409
Calgary, Alberta
Y2N4Y7, Canada

Agent of the Notifier:

Ray A. Matulka, Ph.D.
Burdock Group
801 N. Orange Ave. Suite 710
Orlando, FL 32801
Telephone: 407-802-1400
Facsimile: 407-802-1405
Email: rmatulka@burdockgroup.com

(ii) Common Name of the Notified Substance

The common or usual name of PolyGlycopleX[®] (PGX[®]), for the purposes of this GRAS Notification has been defined as:

Soluble polysaccharide complex

(iii) Trade Name:

The subject of this notification will be marketed as PolyGlycopleX[®] (PGX[®]).

(iv) Conditions of Use

PolyGlycopleX[®] may be used as an ingredient in the food groups shown in Table 1 in order to provide a source of fiber by individuals who desire additional fiber in their diet or to provide texture, thickening, or a stabilizing effect to the food product(s). The levels of use in the stated categories result in consumption of PGX[®] at up to 8,700 mg *per* day.

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Table 1. Food groups selected for PGX[®] supplementation with 14% or less sodium alginate in PGX[®] production

Food Category	Intended use level (ppm)	% PGX[®] in food category	14% Sodium alginate in PGX[®]
		<i>Percentage as served</i>	
Yogurts	11,110	1.11	0.154
Milk shakes and fruit smoothie-type drinks	10,420	1.042	0.146
Frozen yogurt, ice cream bar, and puddings	6,670	0.667	0.092
White and whole wheat breads	50,000	5.0	0.7
Cookies	70,000	7.0	0.98
Breakfast bars	62,500	6.25	0.875
Granola-type bars	62,500	6.25	0.875
Noodles	17,860	1.786	0.25
Whole wheat cereals	70,000	7.0	0.98
Lasagna and macaroni/cheese	10,000	1.0	0.14
Fruit juices and fruit juice bars	10,420	1.042	0.146
Cereal beverage	10,420	1.042	0.146

*The food categories correspond to those listed in 21 CFR §170.3(n). ppm=parts *per* million

(v) Basis of GRAS Determination

Pursuant to 21 CFR §170.3,¹ Inovo Biologic Inc. has, on the basis of advice from its Expert Panel, determined PGX[®] to be generally recognized as safe (GRAS) under the conditions of its intended use as described below and is therefore exempt from the requirement of premarket approval. This finding is on the basis of scientific procedures as described in the notification previously submitted as GRAS Notice (GRN) No. 000328. We are appending to this notification GRN 000328 by reference.

(vi) Availability of Information

The data and information that serve as a basis for this GRAS determination are available for FDA review and copying at reasonable times at:

Burdock Group
 801 N. Orange Ave. Suite 710
 Orlando, FL 32801
 Telephone: 407-802-1400
 Facsimile: 407-802-1405
 Email: rmatulka@burdockgroup.com

Alternatively, data and information that serve as a basis for this GRAS determination will be sent to FDA upon request.

2. Detailed Information about the Identity of the Notified Substance

¹ Title 21 of the US Code of Federal Regulations (CFR), §170.3, year 2011.
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A. Identity

PolyGlycopleX[®] (PGX[®]) is an off-white, granular, soluble polysaccharide fiber complex powder manufactured from konjac glucomannan, sodium alginate, and xanthan gum. The general descriptive characteristics of PGX[®] are presented in Table 2. This complex was previously determined GRAS as a single entity, notified to FDA, and FDA evaluated the GRAS determination of PGX[®] as GRN 000328.

Table 2. General description of PGX[®]

Appearance	Off-white granular powder
Packaging	Tight Container
Storage	25°C
Stability	2 years
Labeling	PolyGlycopleX [®] , PGX [®] , a soluble polysaccharide complex containing xanthan gum, konjac glucomannan and sodium alginate
Functionality in Food	Thickner/firming agent, source of fiber

B. Composition

The chemical composition of PGX[®] is summarized in Table 3. PGX[®] is a mixture of carbohydrates, fiber, ash and protein.

Table 3. Typical analysis of the major components of PGX[®]

Analysis	Batch Analysis Results (n=5)	
	Range	Average
Carbohydrates (%)	80 – 85.4	83.6
Total dietary fiber (%)	82.4 – 91.6	84.74
Ash (total) (%)	5 – 6.2	5.72
Protein (%)	1.8 – 2.2	2.04
Fat (%)	<0.1 – 0.1	<0.1

C. Method of Manufacture of PGX[®]

The manufacturing process is identical to the process outlined in GRN 000328, which provided the schematic and other information that described the process wherein konjac powder, sodium alginate and xanthan gum are initially combined, then through a patented manufacturing process the three food grade ingredients form PGX[®]. A schematic of a manufacturing process has been provided in GRN 000328.

D. Specifications for Food Grade PGX[®]

Specifications provided in Table 4 for PGX[®] include viscosity, lead, arsenic, sodium, potassium, bacteria, yeast and molds, and the absence of *Escherichia coli*, *Salmonella* and *Staphylococcus aureus*, are identical to the specifications stated in GRN 000328.

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Table 4. Specifications for PGX®

Analysis	Method	Specification	Batch Analysis Results (n=5)	
			Range	Average
Viscosity	5 g in 350 ml H ₂ O; Reading in one hour*	>35,000 cP		
Loss on drying (%)	135°C oven	NMT 15	4.20 – 9.08	6.66
Lead (ppm)	ICP	NMT 2	<0.50 – 0.92	0.62
Arsenic (ppm)	ICP	NMT 3	<1.5	<1.5
Sodium (%)	ICP		2.34 – 2.94	2.58
Potassium (%)	ICP	NMT 4	0.41 – 0.80	0.60
Microbiological (cfu/g)				
Standard plate count	USP<61>	NMT 1000	20 - 700	256
Yeast & Mold (cfu/g)	USP<61>	NMT 100	<10	Negative
<i>Escherichia coli</i>	USP<61>	Negative	Negative	Negative
<i>Salmonella spp</i>	USP<61>	Negative	Negative	Negative
<i>Staphylococcus aureus</i>	USP<61>	Negative	Negative	Negative

*Viscosity is measured on a Brookfield type rotational viscometer at room temperature; cfu = colony forming units; cP = centipoise; g = grams; ICP = inductively coupled plasma; n = number of batches analyzed; NMT = not more than; ppm = parts per million; USP = United States Pharmacopeia; methods available upon request

3. Self Limiting Levels of Use

The quantity of PGX® is self-limiting to the extent that it creates a sensation of fullness, similar to any of the conventional soluble fiber food ingredients, and would be limited in consumer acceptance of products when added as a thickener.

4. Basis of GRAS Determination

The determination that PGX® is GRAS is on the basis of scientific procedures, as described in the Dossier in Support of the Generally Recognized as Safe (GRAS) Status of PGX® as a Food Ingredient submitted under GRN 000328. Scientific studies evaluated for the determination of safety of PGX® included a 90-day dietary toxicity study in rats, genotoxicity studies, and clinical trials that analyzed the PGX® complex. This complex was previously determined GRAS as a single entity, notified to FDA, and FDA evaluated the GRAS determination of PGX® as GRN 000328. Following FDA's evaluation, FDA provided a "no basis" letter in response to GRN 000328 concerning the determination of the GRAS status of PGX® when used as a food ingredient in a variety of food categories. The issues stated in the "no basis" letter centered on the FDA conclusion that PGX® (termed "the polysaccharide complex KAX" by FDA) was not a unique chemical entity. FDA stated that:

FDA's evaluation focused both on safety information and whether or not the polysaccharide complex KAX is truly distinct from a mixture of ingredients that are already used in food. FDA considers that the regulations that address the use of individual components in a mixture also address the use of that mixture.

In the "no basis" letter, FDA concluded that "In FDA's view, data provided in the notice do not substantiate that the polysaccharide complex KAX is a new chemical entity, but simply a ternary mixture of variable proportions of konjac, sodium alginate, and xanthan gum."

Based on FDA's conclusion that PGX® was not a single chemical entity, but a mixture of ingredients, the agency referenced the regulations for the individual components that were

utilized in the production of PGX[®] (*i.e.*, konjac, xanthan gum and sodium alginate) to determine if the use of these components were within current FDA regulations. FDA determined that Inovo's intended uses of PGX[®], on the presumption PGX[®] was actually a mixture of the three components, was out of compliance because the amount of sodium alginate in PGX[®] at the intended levels of use, exceeded that permitted by regulation.² That is, under 21 CFR §184.1724(c), current uses of sodium alginate have been affirmed as GRAS, only within specific limitations (Table 5) and in accordance with 21 CFR §184.1(b)(2). Further, 21 CFR §184.1(b)(2) specifies that any use of sodium alginate not in compliance with such established limitations requires a food additive regulation.

Table 5. Limitations of sodium alginate use in food as per 21 CFR §184.1724*

Category of food	Maximum level of use in food (as served) (percent)	Functional use
Condiments and relishes, 170.3(n)(8) of this chapter, except pimento ribbon for stuffed olives	1.0	Texturizer, 170.3(o)(32) of this chapter, formulation aid 170.3(o)(14) of this chapter, stabilizer, thickener, 170.3(o)(28) of this chapter.
Pimento ribbon for stuffed olives	6.0	Do.
Confections and frostings, 170.3(n)(9) of this chapter	0.3	Stabilizer, thickener, 170.3(o)(28) of this chapter.
Gelatins and puddings, 170.3(n)(22) of this chapter	4.0	Firming agent, 170.3(o)(10) of this chapter; flavor adjuvant, 170.3(o)(12) of this chapter; stabilizer, thickener, 170.3(o)(28) of this chapter.
Hard candy, 170.3(n)(25) of this chapter	10.0	Stabilizer, thickener, 170.3(o)(28) of this chapter.
Processed fruits and fruit juices, 170.3(n)(35) of this chapter	2.0	Formulation aid, 170.3(o)(14) of this chapter; texturizer, 170.3(o)(32) of this chapter.
All other food categories	1.0	Emulsifier, 170.3(o)(8) of this chapter; firming agent, 170.3(o)(10) of this chapter; flavor enhancer, 170.3(o)(11) of this chapter; flavor adjuvant, 170.3(o)(12) of this chapter; processing aid, 170.3(o)(24) of this chapter; stabilizer and thickener, 170.3(o)(28) of this chapter; surface active agent, 170.3(o)(29) of this chapter.

*Title 21 of the US Code of Federal Regulations (CFR), year 2011.

The regulation for sodium alginate use in food specifically states that the 1% limitation is the maximum level of use in food (as served), for food categories other than those specifically stated in the regulation, limited to the following functional uses: emulsifier, firming agent, flavor enhancer, flavor adjuvant, processing aid, stabilizer and thickener, or surface active agent. The highly viscous nature of PGX[®] inherently provides thickness and texture to food products.

Therefore, FDA asserts PGX[®] is a mixture and not a single chemical entity, with the limiting factor as the amount of sodium alginate present. In response, this notification limits the amount of PGX[®] to be added to food on the basis of the amount of sodium alginate present in the PGX[®] to be added to any food category.

² 21 CFR §184.1724. Sodium alginate.
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The physical and chemical properties of PGX[®] have been outlined in the GRAS dossier and in GRN 000328. The quantity of sodium alginate utilized in the manufacture of PGX[®] had been stated as a range between 5 – 30% in the GRAS dossier submitted as part of GRN 000328. Inovo is modifying the amount of sodium alginate that may potentially be utilized in the production of PGX[®] to not more than 14% (Table 6).

Table 6. Physical and chemical properties of PGX[®]

Characteristic	Percentage of individual ingredient in PGX[®]
Konjac powder	48-90
Sodium alginate	NMT 14%
Xanthan gum	5-20
Appearance	Granular
Color	Off-white
Particle size	NMT 1% 20 mesh; 60% 40 mesh; NMT 35% 60 mesh; NMT 4% fines less than 60 mesh

NMT=Not more than

The broad range of potential sodium alginate use was defined in early Inovo documents (*e.g.*, patents) so that the ability to utilize sodium alginate to obtain the greatest viscosity would not be limited. Subsequent testing by Inovo found that the addition of sodium alginate to a preparation of xanthan gum and konjac glucomannan synergistically increased the viscosity, with the greatest viscosity reached when sodium alginate was added at levels of 14% or less of the total composition. Therefore, Inovo has restricted the range that sodium alginate may be utilized in the production of PGX[®] to 14% or less. Restricting the range that sodium alginate may be utilized in the production of PGX[®] to 14% or less results in conformance to the sodium alginate limitation in the majority of the food products (Table 1). Analysis of the *percent* of sodium alginate in the food (as served) found that two of the food products (cookies and whole wheat cereals) would still exceed the sodium alginate limitation when PGX[®] was added to these products at up to 83,333 ppm.³ Therefore, Inovo has reduced the intended use level of PGX[®] added to cookies and whole wheat cereals from 83,333 ppm to 70,000 ppm. This change in the intended use levels for PGX[®] in these food products results in an estimated amount of sodium alginate in food (as served) at 0.98%.

Calculations for the daily consumption of PGX[®] when added to the food products stated in the original GRAS notification (GRN 000328) estimated consumption of PGX[®] at 10,070 mg/day at the 90th percentile. A subsequent analysis of the estimated consumption of PGX[®] when added to the intended food products at the revised intended use levels (*i.e.*, 70,000 ppm in cookies and whole wheat cereals) was performed utilizing the National Health and Nutrition Examination Survey (NHANES) 2005-2006 dietary data set to determine the estimated consumption of PGX[®] with the altered use levels. The revised estimated consumption of PGX[®] in the food products indicated in Table 1 has been calculated at 8,700 mg/day at the 90th percentile.

The GRAS dossier for PGX[®] (GRN 000328) described the food groups selected for the addition and the intended levels of PGX[®] use (ppm). The combination of the amount of sodium alginate that could be utilized in the production of PGX[®] (*i.e.*, 5 – 30% stated in the GRAS

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³ 8.333% PGX[®] in food multiplied by 14% sodium alginate in the PGX[®] = 1.17% sodium alginate in the food.

dossier) and the intended use levels of PGX[®] in the various food categories (up to 83,330 ppm in cookies and whole wheat cereals) resulted in the addition of sodium alginate in excess of the “one percent” maximum level of use in food (as served) stated in the US regulations for sodium alginate.⁴ Therefore, in addition to decreasing the amount of sodium alginate that may be utilized in the production of PGX[®] to not more than 14%, the amount of PGX[®] intended to be added to cookies and whole wheat cereals has been reduced from 83,330 ppm to 70,000 ppm (Table 1). When utilized in the production of PGX[®], the sodium alginate added to foods through the addition of PGX[®] at the intended levels of use in the foods indicated in Table 1 will result in a maximum amount of sodium alginate in the foods (as served) at less than one percent. The clarifications on the amount of sodium alginate utilized in the production of PGX[®] and the intended use levels of PGX[®] in the food products stated in Table 1 does not alter the original determination of the GRAS status of PGX[®] as set forth by a Panel of Experts (as indicated in GRN 000328), because the clarifications only decrease the amount of sodium alginate to be used in the production of PGX[®] and decrease the amount of PGX[®] to be added to foods. Therefore, the clarified levels of PGX[®] use still fall within the original determination that PGX[®] is GRAS at the intended levels of use.

Also included in the GRAS notification for PGX[®] is the use of PGX[®] in medical foods, as described in the amendment to the original GRAS determination. The amendment states that PGX[®] would be added to medical foods to such that an aggregate daily intake of PGX[®] would not exceed 13,070 mg, as monitored by the health care provider. Labeling on medical food products (provided as a sole source of the diet) typically indicate that 5-7 servings/day should be consumed. Therefore, 13,070 mg/5 servings equal 2.6 g PGX[®]/serving of a sole source medical food product. Several medical food products marketed as sole source meal replacement products for weight reduction have indicated in labeling statements that the total amount of the medical food/serving weighs approximately 37 g or greater. The 1% limit for sodium alginate in this food equals at minimum 0.37 g sodium alginate. Therefore, 2.6 g of PGX[®] (PGX[®] with 14% sodium alginate) added to a 37 g medical food product results in a maximum consumption of 0.36 g sodium alginate *per* serving and is in compliance with the 1% use limit for sodium alginate.

In summary, clarifications to the original GRAS (submitted to FDA under GRN 000328) on the use level of sodium alginate in the production of PGX[®], along with a reduction of use levels in the cookie and whole wheat cereal products results in the use of sodium alginate in foods to be within the limitations as specified in 21 CFR §184.1724. The clarification of the amount of sodium alginate used in the production of PGX[®] falls within the specifications stated in original GRAS determination, and the safety of PGX[®] is not in question as the preclinical and clinical studies were conducted with PGX[®] produced with sodium alginate levels of 14% or less and the total estimated daily consumption has been reduced from approximately 10,070 mg/day to 8,700 mg/day.

Therefore, whether as single chemical entity or a mixture and the fact that the range of sodium alginate concentrations are incorporated by PGX[®] specifications, the animal test results remain the same. Also, this notification limits the amount of PGX[®] to be added to food on the basis of the amount of sodium alginate present in the PGX[®] to be added to any food category. The amount of PGX[®] to be added to food is equal to or less than that provided for in the original GRAS conclusion which determined that even at higher levels of use, that based on publicly available information, there is consensus among experts qualified by scientific training and experience to evaluate the safety of substances added to food, that there is reasonable certainty that PGX[®] is GRAS under the intended conditions of use.

⁴ 21 CFR §184.1724 Sodium alginate.
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SUBMISSION END

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