Consumer Health and Nutrition

Lonza

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4 October 2019

Citizen Petition

The undersigned, Lonza Inc., respectfully submits this citizen petition under the United States (U.S.) Food and Drug Administration's (FDA) implementing regulation at 21 CFR §10.30 to request the Commissioner of Food and Drugs to amend 21 CFR §101.9(c)(6)(i) so that it includes "arabinogalactan" in the list of dietary fibers stated as part of the definition of dietary fiber.

A. Action Requested

Lonza Inc. respectfully requests that the U.S. FDA amend 21 CFR §101.9(c)(6)(i), as indicated below in **bold font**, to include arabinogalactan to the list of "isolated or synthetic non-digestible carbohydrate(s)," based on its beneficial physiological effect on immune functioning (U.S. FDA, 2019a):

> *"Dietary fiber": A statement of the number of grams of total dietary fiber in a serving, indented and expressed to the nearest gram, except that if a serving contains less than 1 gram, declaration of dietary fiber is not required or, alternatively, the statement "Contains less than 1 gram" or "less than 1 gram" may be used, and if the serving contains less than 0.5 gram, the content may be expressed as zero. 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. Except as provided for in paragraph (f) of this section, if dietary fiber content is not required, and as a result not declared, the statement "Not a significant source of dietary fiber" shall be placed at the bottom of the table of nutrient values in the same type size. The following isolated or synthetic non-digestible carbohydrate(s) have been determined by FDA to have physiological effects that are beneficial to human health and, therefore, shall be included in the calculation of the amount of dietary fiber: [beta]-glucan soluble fiber (as described in 101.81(c)(2)(ii)(A)), psyllium husk (as described in 101.81(c)(2)(ii)(A)(6)), cellulose, guar gum, pectin, locust bean gum, **~~and~~** hydroxypropylmethylcellulose, **and arabinogalactan."***

As a result of the favorable and consistent effects of arabinogalactan on improved immune function, Lonza Inc., is requesting that arabinogalactan be added to the list of dietary fibers stated in 21 CFR §101.9 (C)(6)(i) - U.S. FDA, 2019a.

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B. Statement of Grounds

B.1 Regulatory Background

On 27 May 2016, the FDA published a final rule amending the Nutrition Facts and Supplement Facts Labels regulations ("the final rule") in the *Federal Register* (81 FR 33742) (U.S. FDA, 2016). As part of this regulation, a definition for dietary fiber was provided as follows:

> "*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*." [21 CFR 101.9(c)(6)(i) - U.S. FDA, 2019a]

As per the final rule, 7 non-digestible carbohydrates (NDCs) were determined to have beneficial physiological effects, including: [beta]-glucan soluble fiber [as described in § 101.81(c)(2)(ii)(A)]; psyllium husk [as described in § 101.81(c)(2)(ii)(B)]; cellulose; guar gum; pectin; locust bean gum; and hydroxypropylmethylcellulose (U.S. FDA, 2019a). Since the final rule, 9 additional NDCs were subsequently found to meet the definition of fiber, including mixed plant cell wall fibers (a broad category that includes fibers like sugar cane fiber and apple fiber, among many others), arabinoxylan, alginate, inulin and inulin-type fructans, high amylose starch (resistant starch 2), galactooligosaccharide, polydextrose, resistant maltodextrin/dextrin, and cross-linked phosphorylated RS4 (U.S. FDA, 2018; U.S. FDA, 2019b).

The FDA indicated 2 ways for interested parties to request an additional NDC be added to list of accepted isolated or synthetic NDCs that meet the definition of dietary fiber in 21 CFR § 101.9 (c)(6)(i); either by the submission of a citizen petition to the FDA (21 CFR 10.30) or by the petition process for the authorization of a health claim (21 CFR 101.70), where an NDC that is the subject of an authorized health claim would be considered a dietary fiber (U.S. FDA, 2019a).

This citizen petition describes the results of 3 human intervention studies wherein the beneficial physiological effects of arabinogalactan on immune function were demonstrated. Specifically, in 1 study, a significant decrease in the incidence of common colds was reported (Riede *et al.,* 2013), and in 2 studies, there were increases in immunity following vaccinations (Udani *et al.,* 2010; Udani, 2013).

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B.2 Characterization of Arabinogalactan

B.2.1 Chemical Structure, Dietary Content, Physical Appearance

Arabinogalactan is a highly branched polysaccharide composed of galactose and arabinose units, in the approximate ratio of 6:1, with a highly substituted back bone of β 1-3 linked galactopyranose units and side chains of galactose and arabinose. The larch wood arabinogalactans are a Type II arabinogalactan, the arabino-3, 6-galactans type, which is the most prevalent class of arabinogalactan, and is found in the exudate gums of gymnosperms such as trees of the genus *Larix, and* angiosperms, such as the *Acacia* tree [Stephen, 1983, Vol. 4 Tab 8]. Although arabinogalactan can be derived from the cell wall of plant cells, that which is derived from the larch trees is unique in that it is not bound by protein (Dion *et al.,* 2016). Lonza Inc. manufactures arabinogalactans, marketed as ResistAid™ and FiberAid™, extracted from the wood of tamarack trees; either Eastern Larch Trees (*i.e., Larix laricina*) or Western Larch Trees (*i.e., Larix occidentalis*). The characterization of Lonza's arabinogalactan is provided in Table B.2.1-1.

Table B.2.1-1 Characterization of Arabinogalactan

Common or Commercial Name	arabinogalactan; or galactoarabinan; or arabogalactan; or larch Gum; FiberAid™; ResistAid™
Description	Arabinogalactan is a polysaccharide composed of galactose and arabinose units with a highly substituted back bone of β 1-3 linked galactopyranose units and side chains of galactose and arabinose
Chemical Name	Galactorabinan; L-arabino-D-galactan
CAS Number	9036-66-2
Molecular Formula	$[(C_5H_8O_4)(C_6H_{10}O_5)_6]x$.
Molecular Weight	16,000 - 25,000 Da.
Physical Appearance	ResistAid™: fine, dry, light brown powder; neutral taste and mild pine-like odor. FiberAid™: off-white powder; very low taste and odor
Total Dietary Fiber Content (average)	ResistAid™: mean of 91.3%; FiberAid™: mean of 86.8%, measured by AOAC 2009:01.
Phosphorus Content (average)	ResistAid™: not tested; FiberAid™: 59.5 ppm
Ash Content (average)	ResistAid™: 1.69%; FiberAid™: 3.51%
Carbohydrate Percentage (average)	ResistAid™: 93.23%; FiberAid™: 91.16%
Protein Content (average)	ResistAid™: 0.18%; FiberAid™: 0.18%
Moisture Content (average)	Maximum 6%

CAS = Chemical Abstracts Service number; Da = Daltons; ppm = parts per million.

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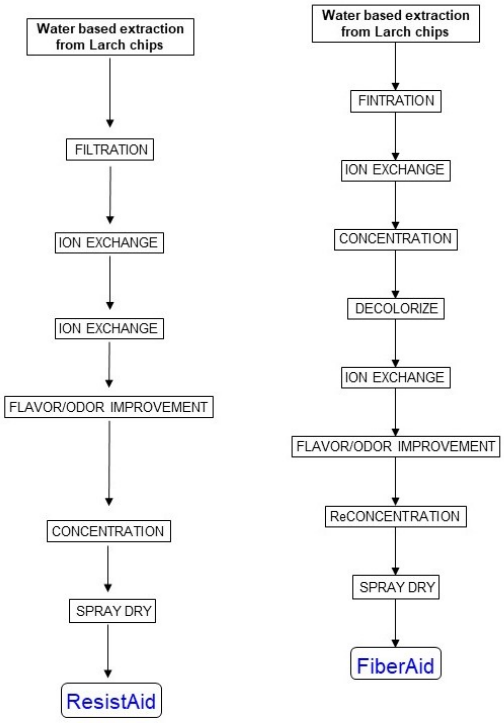
B.2.2 Production Methods

Lonza's arabinogalactan in ResistAid™ and FiberAid™ is commercially extracted from either Eastern or Western larch trees, using water as the only solvent. The processing steps are similar for the production of both products; additional decolorization and flavor/odor improvements are conducted in the production of FiberAid™. Further descriptions regarding the production methods are provided in two Generally Recognized as Safe (GRAS) notifications provided by Larex Inc.[1] (GRN 000047; GRN 000084 – U.S. FDA, 2000, 2002). The mean total dietary fiber content in either ResistAid™ or FiberAid™ is 91.3% and 86.8%, respectively, measured by AOAC 2009:01. A summary of the processing steps is provided in Figure B 2.2-1.

Figure B.2.2-1 Schematic of the Production Methods for ResistAid™ and FiberAid™



B.2.3 Arabinogalactan is Generally Recognized as Safe (GRAS)

Arabinogalactan from *Larix occidentalis* is GRAS for the intended uses in foods in general, including meat products, and for multiple technical effects (*e.g.,* as an emulsifier, formulation aid, humectant, nutrient supplement, processing aid, stabilizer) (Larex Inc. U.S. FDA GRAS 0047 – U.S. FDA, 2000). Arabinogalactan from *Larix laricina* is GRAS for the intended uses in foods in general, including meat and poultry products, and for multiple technical effects.

[1] Larex Inc. was acquired by Lonza Inc.

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B.3 Beneficial Physiological Effect of Arabinogalactans in Humans

Arabinogalactan is an isolated NDC. In order to determine whether or not there exists substantial scientific evidence on arabinogalactan, to support a physiological effect that is beneficial to human health, a comprehensive, transparent, and systematic review of the literature was undertaken, in which only well-controlled human intervention studies were considered. In the FDA guidance document (U.S. FDA, 2018), it is indicated that the FDA would "[…] *intend to consider the publicly available data and written information,* ***primarily from human intervention studies****, regarding the beneficial physiological effect of an added nondigestible carbohydrate."* Furthermore, the FDA indicated that "*We intend to focus our review primarily on articles reporting human intervention studies because these studies can provide evidence from which scientific conclusions can be drawn about the beneficial physiological effect of a specific isolated or synthetic non-digestible carbohydrate in humans*" (U.S. FDA, 2018). The FDA indicated that animal and *in vitro* studies "…*do not provide information from which scientific conclusions can be drawn regarding the beneficial physiological effects in humans of a food component, such as added nondigestible carbohydrates"* (U.S. FDA, 2018) and the FDA intends to use these studies as background to understand the mechanism that might be involved in any physiological beneficial effect of an isolated or synthetic NDC; as such, these studies were excluded during the literature sorting process and did not contribute to the totality of evidence.

B.3.1 Literature Search

To retrieve relevant literature (*i.e.,* human intervention studies) on the effects of arabinogalactan on immune function, 9 literature databases were searched on 9 August 2019 using the electronic search tool ProQuest Dialog™. The databases that were searched, as well as the search terms that were used, are listed in Tables B.3.1-1 and B.3.1-2, respectively. To increase the relevance and specificity of the literature search, the search terms were selected to reflect the dietary fiber of interest (arabinogalactan) and the population of interest (*i.e.,* humans of all ages). No other limitations were placed on the literature search with respect to the publication date, language, and the "fields"[2] searched within the publication.

Table B.3.1-1 Electronic Databases Used to Retrieve Literature

Electronic Database	Date Range of Database
Adis Clinical Trials Insight	1990 to 9 August 2019
Allied and Complementary Medicine™	1985 to 9 August 2019
BIOSIS Previews®	1926 to 9 August 2019
CAB ABSTRACTS	1910 to 9 August 2019
Embase®	1947 to 9 August 2019
Foodline®: SCIENCE	1972 to 2016
FSTA®	1969 to 9 August 2019
MEDLINE®	1946 to 9 August 2019
NTIS: National Technical Information Service	1964 to 9 August 2019

[2] All applicable "fields" were searched, which, for most databases, included the: titles, abstracts, subject, descriptors, category, notes, keywords, and the full-length article (if available in ProQuest Dialog™).

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Table B.3.1-2 Literature Search Strategy

Terms	Strategy
Terms related to exposure	"arabinogalactan" or "ResistAid" or "FiberAid" or "Larix occidentalis" or "larix laricina" or laricina or tamarack
Terms related to outcome	NA
Terms related to study population	men or women or man or woman or human or humans or subject or subjects or participant* or volunteer* or elder* or senior* or geriatric or older or adult* or people or person* or individual* or patient* or child or children or boy or boys or girl or girls or teen* or adolescent* or child* or boy or boys or girl or girls or toddler* or baby or babies or infant or infants or neonat* or clinical or student

Once the search strategy was implemented and the publication titles were retrieved, the relevance of the publications was determined at 3 stages using the titles, abstracts, and the full-texts of publications. At each stage, the inclusion/exclusion criteria listed in Table B.3.1-3 were applied to determine literature relevance. The 3 stages are outlined below in greater detail.

- Stage 1: Titles of articles were reviewed, and abstracts of titles determined to be potentially relevant were retrieved.
- Stage 2: Abstracts were reviewed, and full-length articles of abstracts determined to be potentially relevant were retrieved.
- Stage 3: Full-length articles were reviewed, and those determined not to meet all of the inclusion criteria or to meet any of the exclusion criteria specified in Table B.3.1-3 were excluded.

Table B.3.1-3 Inclusion and Exclusion Criteria for Literature Selection

Inclusion Criteria
• The investigational product was "arabinogalactan" sourced from *L. laricina* or *L. occidentalis* • A full-length article published in a peer-reviewed journal • A randomized controlled trial conducted in humans • The effects of the arabinogalactan on immune function were assessed using clinically relevant endpoints • The study population is generalizable to the American population • The independent effects of the investigational product on the outcome of interest could be isolated

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Table B.3.1-3 Inclusion and Exclusion Criteria for Literature Selection

Exclusion Criteria
• The investigational product was not "arabinogalactan" sourced from *L. laricina* or *L. occidentalis* • The effects of the arabinogalactan on immune function were not assessed or clinically relevant endpoints were not determined • Full-length article published in a non-peer-reviewed source (*e.g.,* website, magazine, *etc.*) • Published in abstract form only (full study report not available) or as a short communication (*e.g.,* letter to the editor, commentary, *etc.*) • Animal or *in vitro* study • Study was not randomized or controlled • Human observational study • Research synthesis study (*e.g.*, narrative review, systematic review, meta-analysis, *etc.*) • The study population was not generalizable to the American population • The independent effects of the investigational product could not be isolated • The study was a duplicate record in the literature search

B.3.2 Literature Search Results

As illustrated in Figure B.3.2-1, the literature search resulted in the identification of 1,006 titles, 961 of which were excluded during title-filtering. Abstracts were retrieved for 45 of the records. Of the 45 abstracts, 38 were excluded, and 7 were considered to be potentially relevant and full-length articles were obtained. Of the 7 full-length articles, 4 studies were excluded (see Table B.3.2-1 for the excluded studies and the reasons for their exclusion), and 3 studies were included (Udani *et al.,* 2010[3]; Riede *et al.,* 2013; Udani *et al.,* 2013[3]) (see Table B.3.2-2 for a list of included references).

[3] The unpublished study reports for 2 of the studies (Udani *et al.,* 2010; Udani, 2013) were also included as references, to substitute relevant information that may not have been included in the respective publications.

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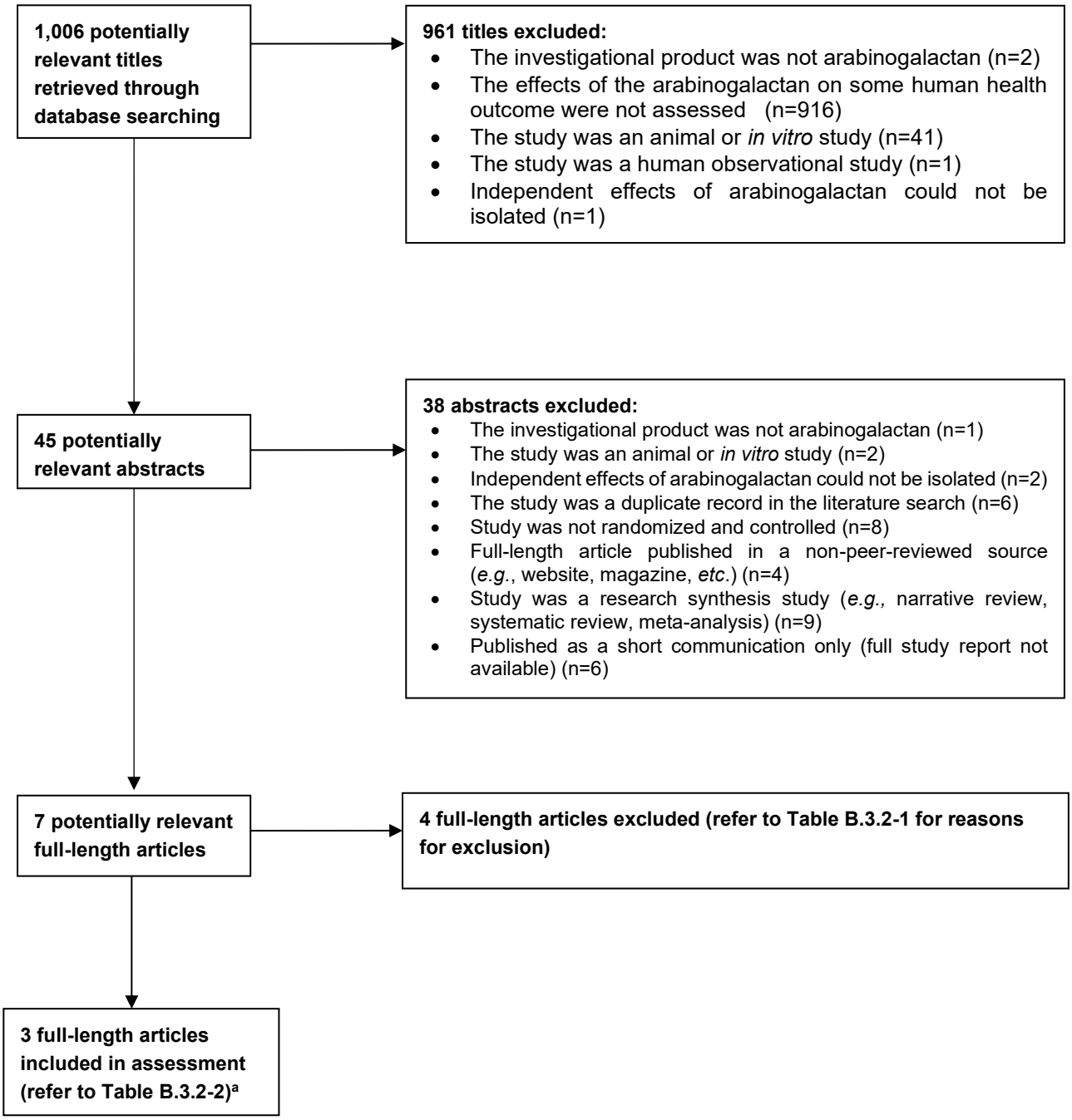
Figure B.3.2.-1 Flowchart of the Literature Search Process



[a] The unpublished study reports for 2 of the studies (Udani *et al.,* 2010; Udani, 2013) are also included as references, to substitute relevant information that may not have been included in the respective publications.

Table B.3.2-1 Excluded Publications at the Full-Length Review Stage and Reasons for Their Exclusion (n=1)

Reference	Reason for Exclusion
Grube B, Stier H, Riede L, Gruenwald J (2012). Tolerability of a proprietary larch arabinogalactan extract: a randomized, double-blind, placebo-controlled clinical trial in healthy subjects. Food Nutr Sci 3(11):1533-1538. DOI:10.4236/fns.2012.311200.	The outcomes were not clinically relevant outcomes related to immune function (n=4)
Kim LS, Waters RF, Burkholder PM (2002a). Immunological activity of larch arabinogalactan and echinacea: a preliminary, randomized, double-blind, placebo-controlled trial. Altern Med Rev 7(2):138-149.	
Kim LS, Burkholder PM, Waters RF (2002b). Effects of low-dose larch arabinogalactan from *Larix occidentalis*: a randomized, double blind, placebo-controlled pilot study. Complement Health Pract Rev 7(3):221-229. DOI:10.1177/153321010200700305.	
Robinson RR, Feirtag J, Slavin JL (2001). Effects of dietary arabinogalactan on gastrointestinal and blood parameters in healthy human subjects. J Am Coll Nutr 20(4):279-285. DOI:10.1080/07315724.2001.10719048.	

Table B.3.2-2 Copies of Included Publications (n=3)

Reference
Riede L, Grube B, Gruenwald J (2013). Larch arabinogalactan effects on reducing incidence of upper respiratory infections. Curr Med Res Opin 29(3):251-258. DOI:10.1185/03007995.2013.765837.
Udani JK (2013). Immunomodulatory effects of ResistAid™: a randomized, double-blind, placebo-controlled, multidose study. J Am Coll Nutr 32(5):331-338. DOI:10.1080/07315724.2013.839907.
Udani JK, Singh BB, Barrett ML, Singh VJ (2010). Proprietary arabinogalactan extract increases antibody response to the pneumonia vaccine: a randomized, double-blind, placebo-controlled, pilot study in healthy volunteers. Nutr J 9(1):32 [7pp]. DOI:10.1186/1475-2891-9-32.
Unpublished Study Reports[a]
Lonza Inc. (2009) [unpublished]. *LONZ1000: Immunomodulatory Effects of a Proprietary Arabinogalactan Extract: A Randomized, Double-blind, Placebo-controlled, Parallel Group Study: Final Report: Confidential*. (June 18, 2009). Prepared by Northridge (CA): Medicus Research LLC for Allendale (NJ): Lonza Inc.[b]
Lonza Inc. (2011) [unpublished]. *LONZ1400 Clinical Study Report: Validation Study of the Immunomodulatory Effects of Resistaid™: A Randomized, Double-blind, Placebo-controlled, Dose-finding Pilot Study: Final Report: Confidential*. (March 25, 2011). Prepared by Northridge (CA): Medicus Research LLC for Allendale (NJ): Lonza Inc.[c]

[a] Unpublished study reports were used to substitute information that was not present in the publication.
[b] Unpublished clinical study report for the study conducted by Udani *et al.* (2010).
[c] Unpublished clinical study report for the study conducted by Udani (2013).

B.3.3 Study Summaries

Three human intervention studies (Udani *et al.,* 2010; Riede *et al.,* 2013; Udani, 2013) were identified, wherein the effects of arabinogalactan on immune functioning in healthy subjects were assessed; a brief summary of the key research aspects of the 3 studies is provided in Table B.3.3-1. A detailed summary of the key characteristics of the 3 clinical studies is provided in Appendix A; an abbreviated summary of the key characteristics is provided in Table B.3.3-2. All 3 studies were randomized, double-blind, placebo-controlled, and parallel in design. The

active investigational product was ResistAid™ in each of the 3 studies; the dose level of 4.5 g/day ResistAid™ was provided to subjects in each of the 3 studies; and, an additional investigational arm of 1.5 g/day ResistAid™ was provided to a different group of subjects in the study by Udani (2013). In each of the studies, the effects of the active investigational product were compared to maltodextrin (MDX), the placebo control.

Table B.3.3-1 A Summary of Relevant Outcomes Related to Immunity Across 3 Human Studies

Reference	Clinically Relevant Outcomes Related to Immune function[a]	
	Incidence, severity, duration of cold	Antibody response to vaccination
Riede *et al.* (2013)	✓[b]	--
Udani *et al.* (2010)	--	✓[c]
Udani (2013)	--	✓[d]

[a] "✓" indicates the outcome was measured in the study while a "--" indicates the outcome was not measured in the study.
[b] Incidence, duration, and severity of a common cold were assessed.
[c] Antibody response to 23-valent pneumococcal vaccine.
[d] Antibody response to tetanus and influenza A/B vaccines.

The study by Riede *et al.* (2013) was conducted in Germany and consisted of a 12-week intervention period (*i.e.,* October 2010 to February 2011) during which healthy subjects were administered an investigational product, according to their random group allocation (*i.e.,* ResistAid™ 4.5 g/day or MDX 4.5 g/day). A total of 199 subjects completed the study; 101 (*i.e.,* 37 males and 64 females) consumed ResistAid™ and 98 (*i.e.*, 28 males and 70 females) consumed MDX. Healthy subjects who had a self- reported cold infection rate of 3 in the last 6 months were recruited in the study. For each group, the mean age [±standard deviation (SD)] and body mass index (BMI) (±SD) were 42.0±14.9 years and 23.7±3.0 kg/m^2 (ResistAid™ group) and 42.4±15.8 years and 24.0±2.7 kg/m^2 (MDX group). Subjects were instructed to dissolve the investigational product in 100 to 150 mL of a liquid of their choice and consume it once per day at breakfast. All eating habits were recorded by subjects in a diary at the start and end of the study, using a 3-day record. During the intervention period, 3 basic visits with research personnel were performed: at baseline (V1), at 6 weeks (V2), and at 12 weeks (V3). Compliance was assessed by counting returned sachet packets (*i.e.,* the accepted compliance rate was defined as 75 to 125% of the investigational products consumed). The objective of the study was to determine the frequency of common cold episodes (*i.e.,* the number of common cold episodes during the study period) between groups, and these were recorded in each subject's diary; each common cold occurrence was investigated by a doctor on the first and fifth day of the episode. Additionally, the duration of cold episodes was recorded; this was defined as the number of days since the cold episode start until the first symptom-free day – findings were based on subject diary recording. Subject's also assessed the intensity of each common cold episode; the participants had to rate and record (in a diary) 10 predefined cold symptoms during the infection episode, on a rating scale (0 = complaint free, 1 = weak symptoms, 2 = moderate symptoms, 3 = strong symptoms). Symptoms were as follows: headache, joint pain, sore throat, difficulty swallowing, hoarseness, coughing, a watery nasal discharge, nasal congestion, cold-related sleeping difficulties, body temperature >38°C. By summing the scores of the individual symptoms, a sum of scores (=total score) was calculated at episode start and after 5 days. Lastly, physiological parameters (*i.e.,* body

weight, temperature, heart rate, blood pressure) were assessed at the start and at the end of the study, and the subjective efficacy of the investigational product was rated by both the participants and the investigator at the end of each common cold episode.

The study conducted by Udani *et al.* (2010) was conducted in the U.S. and consisted of a 72-day intervention period, during which healthy subjects were administered an investigational product according to their random group allocation (*i.e.,* ResistAid™ 4.5 g/day or MDX 4.5 g/day). A sample size of 50 persons was attempted, in order to be consistent with prior human studies involving arabinogalactan and the immune system (Causey *et al.,* 1999; Nantz *et al.,* 2001; Kim *et al.,* 2002). A total of 45 subjects completed the study; 21 (*i.e.,* 9 males and 12 females) consumed ResistAid™ and 24 (*i.e.,* 16 males and 8 females) consumed MDX. For each group, the mean age±SD was 33.52±not reported (NR) years (ResistAid™ group) and 38.25±NR years (MDX group). Although BMI was NR as a mean for each group, all subjects enrolled in the study were required to have a BMI ≥18 kg/m^2 and ≤30 kg/m^2. Subjects were to dissolve the investigational product in 100 to 150 mL of a liquid of their choice and consume it once per day at breakfast. During the supplementation period, the subjects visited the research clinic a total of 5 times [visit (V) 1 to V5] over 72 days: V1 (Day 0): screening visit; V2 (Day 30): vaccine visit [*i.e.,* subjects received the 23-valent pneumococcal vaccine (Pneumovax® 23, Merck and Co., Inc., USA)]; V3 (Day 31): safety monitoring visit (*i.e.,* observation of the reaction at the vaccine administration site); V4 (Day 51) and V5 (Day 72): follow-up visits. On study visits, blood, urine, and saliva were collected and subjects were queried regarding any change in health status. Additionally, compliance to the study protocol was assessed by interview, diary review, and through the return of unused study product sachets. The primary objective of the study was to assess the changes in immune response to the 23-valent pneumococcal vaccine. In consultation with the University of California, Los Angeles (UCLA) Vaccine Center (Torrance, CA, USA), the antibodies most likely to respond to vaccination with the 23-valent pneumococcal vaccine were determined (*i.e.,* IgG 4, 6B, 9V, 14, 18C, 19F, and 23F), and these were measured and assessed on V1, V4, and V5 for all subjects consuming the investigational products. Additionally, salivary immunoglobulin (Ig) A, white blood cell counts, complement C3 and C4 levels and inflammatory cytokine levels also were assessed.

The study conducted by Udani (2013) was conducted in the United States and consisted of a 60-day intervention period during which healthy subjects were administered an investigational product according to their group allocation (*i.e.,* ResistAid™ 1.5 g/day + 3.0 g MDX, ResistAid™ 4.5 g/day, or MDX 4.5 g/day). A total of 75 subjects completed the study; 27 subjects consumed ResistAid™ 1.5 g + 3.0 g MDX, 25 subjects consumed ResistAid™ 4.5 g/day, and 23 subjects consumed MDX; this was in line with the number of subjects included in each group for the study completed by Udani *et al.* (2010). The mean age of subjects in each group was 31.0 years (Group I, consumption of ResistAid™ 1.5 g + 3.0 g MDX); 32.2 years (Group II, consumption of ResistAid™ 4.5 g/day) and 38.4 years (Group III, consumption of MDX), and study inclusion criteria required that subjects had a BMI ≥18 kg/m^2 and ≤30 kg/m^2. Subjects were to dissolve the investigational product in 8 oz. of a cold beverage of their choice and consume it once per day at breakfast. During the intervention period, the subjects visited the research clinic a total of 5 times (V1 to V5): V1 (Day 0): screening – measurement of baseline blood influenza A and B IgM and IgG levels, as well as tetanus IgG levels and subjects were counseled not to change their diet or exercise level during the study – the first dose of the assigned study product was provided to subjects and subjects also

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received a study-dosing diary. On Day 15, subjects were called to check on compliance and to be reminded of their next visit. V2 (Day 30), subjects were administered the tetanus and influenza vaccines *via* intramuscular injection; V3 (Day 31): subjects returned for a safety review of the vaccination site; V4 (Day 45) and V5 (Day 60): blood was drawn for measures of influenza A and B IgM and IgG levels and tetanus IgG levels. Additionally, compliance to the study protocol was assessed by interview, diary review, and through the return of unused study product sachets. The primary objective of the study was to assess the changes in immune response to each of the tetanus (*i.e.,* IgG) and influenza A and influenza B (*i.e.,* IgG and IgM) vaccines, and these were measured on V1, V4, and V5 for all subjects consuming the investigational products.

Table B.3.3-2 Abbreviated Summary of Study Characteristics (n=3)

Reference	Study Design Duration Country of Conduct	Groups/Treatments Dietary Intervention Nutritional Composition of Test Food	Study Participants	Immune Outcomes Assessed[a]	
				Clinically Relevant Outcomes (*e.g.,* incidence, severity, duration, Ab response to vaccination)	Other
Riede *et al.* (2013)	R, DB, PC, P 12 wk: (V1: baseline, V2: 6 wk, V3: 12 wk and Day 1 and Day 5 of a suspected common cold) Germany	ResistAid™ 4.5 g ResistAid™ (sachet) in 100–150 mL of liquid 1X daily at breakfast	n_i = 102[b] (GD NR); n_f = 101[c] (37M, 64F) Age (±SD): 42.0±14.9 y BMI (±SD): 23.7±3.0 kg/m^2	• **Frequency of common cold episodes[d]** – diary documentation Diary recorded measures[e]: • Duration of cold episodes[f] • Cold episode intensity[g] • Cold episode intensity at start of episode[h] • No. of symptom free days	• Biochemical Parameters (baseline and after 12 wk)
		Placebo 4.5 g MDX (sachet) in 100–150 mL of liquid 1X daily at breakfast	n_i = 99[i] (GD NR) n_f = 98[j] (28M, 70F) Age (±SD): 42.4±15.8 y BMI (±SD): 24.0±2.7 kg/m^2		
Udani *et al.* (2010)	R, DB, PC, P 72 d: [V1(d0): screening; V2(d30): vaccine[k]; V3(d31): safety evaluation; V4(d51) & V5(d72): follow-up] U.S.	ResistAid™ 4.5 g ResistAid™ (sachet) in 100–150 mL of liquid 1X daily at breakfast	n_i = NR[l] n_f = 21 (9M, 12F) Age (±SD): 33.52±NR y BMI (±SD): NR[m]	• **Changes in markers of immune response:** ○ **IgG Abs[n]** (*i.e.,* 4, 6B, 9V, 14, 18C, 19F and 23F) – measured on V1, V4 and V5.	• Salivary IgA • WBC counts (totals and subtypes) • Complement (C3, C4) levels • Inflammatory cytokine levels
		Placebo 4.5 g MDX (sachet) in 100–150 mL of liquid 1X daily at breakfast	n_i = NR[l] n_f = 24 (16M, 8F) Age (±SD): 38.25±NR y BMI (±SD): NR[m]		

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Table B.3.3-2 Abbreviated Summary of Study Characteristics (n=3)

Reference	Study Design Duration Country of Conduct	Groups/Treatments Dietary Intervention Nutritional Composition of Test Food	Study Participants	Immune Outcomes Assessed[a]	
				Clinically Relevant Outcomes (*e.g.*, incidence, severity, duration, Ab response to vaccination)	**Other**
Udani (2013)	R, DB, PC, P 60 d: (V1(d0): screening, baseline Ab levels[o]; V2(d30): vaccine[p]; V3(d31): safety evaluation; V4(d45) & V5(d72):follow-up) U.S.	Group I 1.5 g ResistAid™ + 3.0 g placebo (sachet) in 8 oz cold beverage 1X daily at breakfast	n_i = 29 (GD NR) n_f = 27[q] (GD NR[r]) Age (±SD): NR[r] (18–60 y) BMI (±SD): NR[m]	• **Changes in markers of immune response[s]** (measured on V1, V4 and V5)**:** ○ **Tetanus: plasma IgG** ○ **Influenza A: plasma IgM, IgG** ○ **Influenza B: plasma IgM, IgG**	• --
		Group II 4.5 g ResistAid™ (sachet) in 8 oz cold beverage 1X daily at breakfast	n_i = 26 (GD NR) n_f = 25[q] (GD NR[r]) Age (±SD): NR[r] (18–60 y) BMI (±SD): NR[m]		
		Group III 4.5 g MDX (sachet) in 8 oz cold beverage 1X daily at breakfast	n_i = 25 (GD NR) n_f = 23[q] (GD NR[r]) Age (±SD): NR[r] (18–60 y) BMI (±SD): NR[m]		

Ab = antibody; BMI = body mass index; d = day; DB = double blind; F = females; GD = gender distribution; Ig = immunoglobulin; ITT = intention-to-treat; n_f = number of final participants; n_i = number of participants at the trial initial start date; M = males; MDX = maltodextrin; No. = number; NR = not reported; P = parallel; PC = placebo-controlled; PP = per protocol; R = randomized; SD = standard deviation; U.S. = United States; V = visit; WBC = white blood cells; wk = weeks; y = years.

[a] Primary objectives are listed in bold font.
[b] 104 subjects were allocated to receive the active investigational product; 2 subjects presented with abnormal laboratory values; only n=102 actually received the product.
[c] ITT population was n=101; PP population was n=97.

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[d] Frequency of common cold episodes was defined as **the number of common cold episodes during the study period**. The sample size calculation, based on 2 sample t-tests, was determined by the effect size (group comparison), as well as the previously determined requirements of the significance level (5.0%, 2-sided) and power (80%). The assumption of the effect size was based on the results of an unpublished superiority clinical study with a comparable design with an effect size of 0.49 for full analysis set and 0.42 for the PP population. All common cold episodes were confirmed by medical doctors; additional visits occurred at the start and on the fifth day of each common cold episode.

[e] For assessment of episode intensity, the participants had to rate and record (in a diary) 10 predefined cold symptoms during the infection episode, on a rating scale (0 = complaint free, 1 = weak symptoms, 2 = moderate symptoms, 3 = strong symptoms). Symptoms were as follows: headache, joint pain, sore throat, difficulty swallowing, hoarseness, coughing, a watery nasal discharge, nasal congestion, cold-related sleeping difficulties, body temperature >38°C. By summation of the scores of the individual symptoms, a sum of scores (=total score) was calculated at episode start and after 5 d.

[f] The duration of an episode was defined as the number of days since episode start until the first symptom-free day – findings were based on subject diary recording.

[g] Calculated as the change of the total sum score after 5 days compared to start of episode at first episode visit, based on case report file and subject diary.

[h] Episode intensity sum score on Day 1 based on subject diary.

[i] A total of 100 subjects were allocated to receive the placebo investigational product; 1 subject presented with abnormal laboratory values; only n=99 actually received the product.

[j] ITT population was n=98; PP population was n=90.

[k] 23-valent pneumococcal vaccine.

[l] 45 subjects were included in the ITT analysis.

[m] All recruited subjected were screened to have a BMI ≥18 kg/m^2 and ≤30 kg/m^2.

[n] In consultation with the UCLA Vaccine Center (Torrance, CA, U.S.), the Abs most likely to respond to vaccination with the 23-valent pneumococcal vaccine were determined. As there was no prior human data regarding the ability of this proprietary arabinogalactan extract to impact the immune response to the pneumococcal vaccine, a power calculation could not be performed. The sample size was set at a level consistent with prior human studies involving arabinogalactan and the immune system

[o] Measurement of baseline blood influenza A and B IgM and IgG levels as well as tetanus IgG levels.

[p] Tetanus and Influenza A/B vaccines.

[q] In each of the 3 groups, subjects dropped out of the respective groups early (ResistAid™ 1.5g: n=2; ResistAid™ 4.5g: n=1; Placebo: n=2).

[r] Baseline characteristics for gender, age, ethnicity or marital status did not differ between groups.

[s] Sample size calculation was NR.

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B.3.4 Results of Studies

Detailed tabular summaries of the results of the studies are presented in the subsequent sections of this report (*i.e.,* Sections B.3.4.1-B.3.4.3). Clinically relevant study results related to immunity are reported on and discussed; the consistency and statistical significance of the results – which are the 2 most important criteria in the evaluation of causality – are discussed. All study results are reported for the intention-to-treat (ITT) population group, unless otherwise specified.

Although the FDA does not provide formal guidance on immune-related endpoints that would be considered clinically relevant, the European Food Safety Authority (EFSA) released a guidance document in 2016 titled, "*Guidance on the scientific requirements for health claims related to the immune system, the gastrointestinal tract and defense against pathogenic microorganisms"* (hereinafter referred to as the "EFSA Guidance Document"), in which relevant endpoints related to immune function for the purpose of submitting a health claim application in the European Union were highlighted (EFSA, 2016). Some important general considerations discussed in the document are highlighted below:

- "*The scientific evidence for the substantiation of health claims related to defense against pathogens can be obtained from human intervention studies showing an effect on clinical outcomes related to infections (e.g. incidence, severity and/or duration of symptoms). The infectious nature of the disease should be established, e.g.* ***by clinical differential diagnosis*** *alone or in combination with microbiological data and/or the use of validated questionnaires[4], depending on the study context and type of infection*."

- "[…] *upper or lower respiratory tract infections clinically diagnosed by the primary care or hospital physician following well defined criteria can be used as an appropriate outcome variable for the scientific substantiation of the claim, provided that adequate exclusion criteria for the most common non-infectious causes (e.g. allergic diseases) of the signs and symptoms used for diagnosis of the respiratory infection have been applied (i.e. differential diagnosis)*".

- "*Vaccination confers immunity to certain infectious diseases. Even if a strict correlation between antibody titers in response to vaccination and protection against infection is not always evident, cut-off values of antibody titers in response to vaccination indicating protection have been established for many vaccines. An increase in the number of responders to vaccination (i.e. attaining antibody titers beyond a cut-off value which is considered to protect against the infection) is an appropriate outcome variable for the scientific substantiation of claims related to immune defense against pathogens*."

[4] EFSA indicates that a main weakness of human intervention studies submitted for the substantiation of claims against pathogens in the upper respiratory tract was the use of non-validated questionnaires on self-reported symptoms, in order to assess the incidence, severity/duration of common cold episodes.

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- "*Other outcome variables, such as changes in relevant immunological markers, may provide supportive evidence on the mechanism (e.g. through the activation of the immune system) by which the food/constituent could exert the claimed effect, but alone are not appropriate outcome variables for the substantiation of claims related to immune defense against pathogens*."

- *"With respect to the study group, subjects without an infection at baseline, including subjects at high risk for infection without an infection at baseline (e.g. travelers to high risk countries, subjects under intense physical exercise, elderly individuals in nursing homes, children attending day-care centers, subjects challenged with live viruses/bacteria) could be suitable study groups for the scientific substantiation of claims on (immune) defense against pathogens for the general population, as long as the methods and the inclusion/exclusion criteria used to characterize the study group in relation to the absence of ongoing infectious diseases at baseline are clearly defined*."

B.3.4.1 Effects of Arabinogalactan on the Incidence of Common Colds

Across 1 stratum (1 publication), the effect of arabinogalactan on the incidence of common colds (*i.e.,* the number of common colds experienced during the study period) was assessed (i) using a subjective diary (subjects indicated when they felt that they were experiencing a common cold); and (ii*) via* an assessment by a medical doctor on the first and fifth day of a suspected common cold episode (Table B.3.4.1-1). Healthy subjects who had consumed ResistAid™, compared to subjects who had consumed MDX, experienced (mean±SD) 0.83±0.82 *versus* 1.06±0.85 colds, respectively, over the study duration (*i.e.,* October 2010 to February 2011); a near significant reduction (P=0.055) was observed in the mean number of common colds for the group consuming the active investigational product *versus* placebo. The authors noted that in the per protocol (PP) population, a significant reduction (P=0.040) in the number of common colds was observed between those consuming the active investigational product and those consuming the placebo. A total of 12 subjects (*i.e.*, n=4 in the ResistAid™ group; n=8 in the placebo group) were removed from the full analysis set of individuals to form the PP set, due to protocol deviations.

Additionally, the number of participants affected by a cold episode during the intervention period was reported (Table B 3.4.1-2). As indicated in Table B 3.4.1-2, a significant reduction (P=0.038) in the number of persons experiencing at least 1 common cold episode was observed between those consuming ResistAid™ (n=59; 58%) *versus* those consuming the placebo (n=71; 72%).

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Table B.3.4.1-1 Quantitative and Statistical Results on the Effects of Arabinogalactan on the Incidence of Common Cold Episodes[a,b]

Reference	Duration	Active Group			Placebo Group			Placebo Adjusted Effect	P-Value bw Groups
		Investigational Product and Daily Dose	No. of subjects	Mean number of common cold episodes (±SD) (CI)	Investigational Product and Daily Dose	No. of subjects	Mean number of common cold episodes (±SD) (CI)		
Riede *et al.* (2013)	12 wk	4.5 g ResistAid™ (in sachet) dissolved in 100–150 mL of liquid, 1X/d	n_i = 102 (GD NR) n_f = 101 (37M, 64F)	0.83±0.82 (0.89–1.29)	4.5 g MDX (in sachet) dissolved in 100–150 mL of liquid, 1X/d	n_i = 99 (GD NR) n_f = 98 (28M, 70F)	1.06±0.85 (0.89–1.23)	*-0.23 ± 0.03*	0.055

bw = between; CI = confidence interval; d = day; F = females; GD = gender distribution; M = males; MDX = maltodextrin; nf = final number of participants; ni = initial number of participants; No. = number; NR = not reported; SD = standard deviation; wk = weeks.

[a] Frequency of common cold episodes was defined as **the number of common cold episodes during the study period.** All common cold episodes were confirmed by medical doctors during the 12-wk intervention period; in addition to the pre-planned study-related visits, additional visits occurred at the start and on the fifth day of each common cold episode.

[b] All italicized values were calculated from information provided in the publication.

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Table B.3.4.1-2 Quantitative and Statistical Results on the Effects of Arabinogalactan on the Number of Participants Affected by a Cold Episode[a]

Reference	Duration	Active Group			Placebo Group			Placebo Adjusted Effect	P-Value bw Groups
		Investigational Product and Daily Dose	No. of subjects	No. of subjects experiencing ≥1 cold episode (%)	Investigational Product and Daily Dose	No. of subjects	No. of subjects experiencing ≥1 cold episode (%)		
Riede *et al.* (2013)	12 wk	4.5 g ResistAid™ (in sachet) dissolved in 100–150 mL of liquid, 1X/d	n_i = 102 (GD NR) n_f = 101 (37M, 64F)	59 (58%)	4.5 g MDX (in sachet) dissolved in 100–150 mL of liquid, 1X/d	n_i = 99 (GD NR) n_f = 98 (28M, 70F)	71 (72%)	*-12*	**0.038**

bw = between; d = day; F = females; GD = gender distribution; M = males; MDX = maltodextrin; n_f = final number of participants; n_i = initial number of participants; No. = number; NR = not reported; wk = weeks.
[a] All italicized values were calculated from information provided in the publication.

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B.3.4.2 Effects of Arabinogalactan on the Intensity, Severity, and Duration of Common Colds

Riede *et al.* (2013) also reported on the intensity, severity and duration of common cold episodes, as well as the number of symptom-free days. These outcomes were not outlined in this citizen peition, as the use of rescue medication was not controlled for; outcomes other than incidence are difficult to interpret, due to the lack of control over rescue medication.

B.3.4.3 Effects of Arabinogalactan on Conferring Immunity Following Vaccination

Across 3 strata (2 publications), the effect of consuming ResistAid™ on immunity following vaccination was reported. In the study by Udani *et al.* (2010), the immune response following a 23-valent pneumococcal vaccine was reported, while in the study by Udani (2013), immunity following both a tetanus and influenza A/B vaccine was assessed.

Udani *et al.* (2010) assessed the effects of arabinogalactan on 7 IgG antibodies (*i.e.,* type 4, 6B, 9V, 14, 18C, 19F, 23F), 51 and 72 days following vaccination with a 23-valent pneumococcal vaccine. The authors discuss results for 2 of the 7 antibodies (*i.e.,* IgG types 18C and 23F) (Table B.3.4.3-1). A significant increase in antibody titers for IgG 18C at both 51 days (P=0.006) and 72 days (P=0.008) post vaccination was observed in subjects who consumed 4.5 g/day ResistAid™ compared to placebo. Furthermore, the changes in IgG 18C antibody titer from Days 0 to 52 and Days 0 to 72 were significantly greater in the group that consumed ResistAid™ *versus* placebo, P=0.033 and P=0.012, respectively. The same trend was observed for IgG 23F. Significant increases in antibody titers for IgG 23F at both 51 (P=0.002) and 72 days (P=0.041) post vaccination were observed in subjects who consumed ResistAid™ compared to placebo. Furthermore, the changes in IgG 23F antibody titers from Days 0 to 52 and Day 0 to 72 were significantly greater in the group that consumed ResistAid™ *versus* placebo, P=0.001 and P=0.001, respectively. Additionally, the authors reported the antibody titer levels for some of the other IgG types measured; *change scores from baseline and mean values were greater in the arabinogalactan group than the placebo group for most time points in IgG types 4, 6B, 9V an 19F, but levels were not significantly different between groups.*

In the study by Udani (2013), the effects of ResistAid™ consumption on immunity following both a tetanus and Influenza A/B vaccine were assessed. Antibody IgG levels were measured and reported on as 1 group. With respect to the tetanus vaccine, the author indicated that no significant changes in immunity were observed at any time point [*i.e.,* at baseline (p=0.172), 45 days (p=0.363), or 60 days (p=0.160) following vaccination] between those who consumed 4.5 g/day ResistAid™ and placebo. However, for the group that consumed 4.5 g/day ResistAid™, Udani (2013) noted that significant increases in IgG titers were observed, compared to baseline values, at 45 days post vaccination, with further increases in IgG levels noted at 60 days post vaccination, while IgG levels in both the placebo and 1.5 g/day ResistAid™ groups peaked at 45 days. Udani indicated that a significant increase (p=0.008) was observed between tetanus IgG antibody titers at Day 60 for subjects consuming 1.5 g/day ResistAid™ (mean±SD) (4.04±2.314 IU/mL*) versus* those consuming the placebo (mean±SD) (3.69±1.609 IU/mL), but no differences were observed between these groups at baseline (p=0.228) or at 45 days post vaccination (p=0.207). Results are reported in Table B.3.4.3-1.

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In the same study, conducted by Udani (2013), results regarding the effect of ResistAid™ consumption on immunity following the Influenza A/B vaccine, in comparison to placebo consumption, were reported. For each of the groups consuming ResistAid™, either 1.5 g/day or 4.5 g/day, in comparison with placebo, no differences were noted at 45 days or 60 days post vaccination for Influenza A IgG, Influenza B IgG or IgM. Additionally, no differences were noted for Influenza IgM immunity at 45 or 60 days post vaccination, between the groups consuming ResistAid™ at 4.5 g/day *versus* placebo. A significant increase in immunity to Influenza A IgM was observed at 45 days post vaccination in the group consuming placebo *versus* ResistAid™; however, no difference between groups was observed 60 days post vaccination.

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Table B.3.4.3-1 Quantitative and Statistical Results on the Effects of Arabinogalactan on the Vaccination Immunity

Reference	Duration Vaccine	Active Group Investigational Product and Daily Dose	No. of subjects	IgG response Day	IgG	Placebo Group Investigational Product and Daily Dose	No. of subjects	IgG response Day	IgG	Placebo Adjusted Effect	P-Value bw Groups
Udani *et al.* (2010)	72 d 23-valent pneumo coccal vaccine	ResistAid™ 4.5 g ResistAid™ (sachet) in 100–150 mL of liquid 1X/d	n_i = NR n_f = 21 (9M, 12F)	IgG 18C (**µg/ml ±SD**)		Placebo 4.5 g MDX (sachet) in 100–150 mL of liquid 1X/d	n_i = NR n_f = 24 (16M, 8F)	IgG 18C (**µg/mL ±SD**)		IgG 18C	
				0	0.0149±0.03			0	0.0072±0.0135	*0.0077 ±0.061*	0.061
				51	0.0957±0.0796			51	0.0506±0.058	*0.0451 ±0.0216*	**0.006**
				72	0.091±0.0753			72	0.0493±0.0596	*0.0417 ±0.0227*	**0.008**
				0–51	0.0808±0.0712			0–51	0.0434±0.051	*0.0374 ±0.0202*	**0.033**
				0–72	0.0761±0.0681			0–72	0.0422±0.0469	*0.0339 ±0.0212*	**0.012**
				IgG 23F				IgG 23F		IgG 23F	
				0	0.0074±0.0093			0	0.0108±0.0187	*-0.0034 ±0.0094*	0.059
				51	0.0707±0.0741			51	0.0432±0.0462	*0.0275 ±0.0279*	**0.002**
				72	0.0702±0.0731			72	0.0455±0.0523	*0.0247 ±0.0208*	**0.041**
				0–51	0.0633±0.0736			0–51	0.0324±0.0428	*0.0309 ±0.0308*	**0.001**
				0–72	0.0628±0.0717			0–72	0.0346±0.0442	*0.0282 ±0.0275*	**0.001**

Table B.3.4.3-1 Quantitative and Statistical Results on the Effects of Arabinogalactan on the Vaccination Immunity

Reference	Duration	Active Group				Placebo Group				Placebo Adjusted Effect	P-Value bw Groups
	Vaccine	Investigational Product and Daily Dose	No. of subjects	IgG response Day	IgG	Investigational Product and Daily Dose	No. of subjects	IgG response Day	IgG		
Udani (2013)	60 d Tetanus vaccine	Group I 1.5 g ResistAid® + 3.0 g placebo (2X1.5 g sachets) dissolved in 8 oz cold beverage, 1X/d	n_i = 29 (GD NR) n_f = 27 (6M, 21F)	IgG (IU/mL ± SD)		Group III: Placebo 4.5 g MDX (3X1.5 g sachets) dissolved in 8 oz cold beverage, 1X/d	n_i = 25 (NR) n_f = 23 (6M, 17F)	IgG (IU/mL ± SD)		IgG	
				0	1.85±1.607			0	1.45±1.224	*0.4 ±0.383*	0.228
				0–45	4.41±2.217			0–45	4.14±1.942	*0.27±0.275*	0.207
				0–60	4.04±2.314			0–60	3.69±1.609	*0.35±0.705*	**0.008**
		Group II 4.5 g ResistAid™ (3X1.5 g sachets) dissolved in 8 oz cold beverage, 1X/d	n_i = 26 (NR) n_f = 25[q] (9M, 15F	0	2.23±1.939	Group III: Placebo 4.5 g MDX (3X1.5 g sachets) dissolved in 8 oz cold beverage, 1X/d	n_i = 25 (NR) n_f = 23 (6M, 17F)	0	1.45±1.224	*0.78±0.715*	0.172
				0–45	4.59±2.256			0–45	4.14±1.942	*0.45±0.314*	0.363
				0–60	4.62±2.135			0–60	3.69±1.609	*0.93±0.526*	0.160

bw = between; d = day; F = females; Ig = immunoglobulin; IU = international unit; M = males; MDX = maltodextrin; n_f = final number of participants; n_i = initial number of participants; No. = number; NR = not reported; SD = standard deviation.
[a] All italicized values were calculated from information provided in the publication.
[b] All values underlined were converted to appropriate units for clarity of results.

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B.3.5 Overall Conclusions on the Scientific Evidence

B.3.5.1 Effects of Arabinogalactan on the Incidence of Common Colds

In the study conducted by Riede *et al.* (2013), 2 clinically relevant outcomes for immune function were outlined with respect to the incidence of common colds:

- A significant reduction (P=0.038) in the number of persons experiencing at least 1 cold throughout the study period (*i.e.,* 12 weeks) was reported in the study group consuming ResistAid™ (n = 59; 58%) *versus* the placebo (n = 71; 72%) (Riede *et al.,* 2013).

- The mean number of common colds experienced during the 12-week study period was lower [albeit not quite significant (P=0.055)] in the ITT population group, between those consuming ResistAid™ (mean±SD) (0.83±0.82) *versus* those consuming placebo (mean±SD) (1.06±0.85). The difference did reach significance (P=0.040) when the PP population was reviewed rather than the ITT population. The PP population excluded from analyses n=8 individuals who were reported to have protocol deviations (Riede *et al.,* 2013).

B.3.5.2 Effects of Arabinogalactan on Vaccination Immunity

Across 3 strata and 2 publications (Udani *et al.,* 2010; Udani, 2013), the effect of arabinogalactan on immunity following standardized vaccinations was evaluated.

- Consumption of ResistAid™ at 4.5 g/day lead to an increase in immunity following the 23-valent pneumococcal vaccine for both IgG 18C and 23F subtypes (Udani *et al.,* 2010). Although controversy exists regarding the exact value which constitutes an adequate serotype-specific antibody response following immunization with this vaccine (Daly and Hill, 2015; Remschmidt *et al.,* 2016; Andrews *et al.* (2014) indicate an estimated correlate of protection in the range of 0.14 and 0.20 µg/mL for serotypes 18C and 23F. Using these cut-off values, immunity was achieved in both groups (those consuming ResistAid™ or placebo), but to a significantly greater extent in the group consuming ResistAid™.

- Consumption of ResistAid™ at 1.5 g/day, in comparison with consumption of placebo MDX, lead to a significant increase (p=0.008) in immunity following the tetanus vaccine for IgG antibodies (Udani, 2013). All post-vaccination IgG titers were higher than 2.5 IU/mL, the value generally recognized as adequate to confer immunity to the tetanus vaccine, when pre-vaccination IgG titers are higher than 1.0 IU/mL (ARUP Laboratories, 2019). Therefore, immunity was adequate in each group, and was significantly higher in the group that consumed 1.5 g/day ResistAid™ *versus* placebo.

Overall, the results of the studies suggest that ResistAid™ (*i.e.,* larch arabinogalactan) improves immunity by increasing immunoglobulin response following a standard vaccine challenge (*i.e.,* tetanus and 23-valent pneumococcal vaccine) and by decreasing infections (*i.e.,* incidence of colds,). Therefore, arabinogalactan meets the definition of a dietary fiber in the U.S., as outlined by the

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FDA, because it is an NDC with 3 or more monomeric units that, based on the evidence described herein, confers a beneficial physiological effect to human health, namely, *an improvement in immune function.*

B.3.5.3 Discrepancies and Possible Explanations to Consider

- In the study conducted by Udani (2013), a dose of 4.5 g/day ResistAid™ did not confer a greater immunity following the tetanus vaccine *versus* placebo; significant differences were observed in the group wherein 1.5 g/day ResistAid™ was consumed. In this group, it is important to note that over time, compared to baseline values, significant increases in IgG titers were seen at 45 days post vaccination, with further increases at 60 days post vaccination, even though both the IgG in the placebo and 1.5 g/day ResistAid™ groups peaked at 45 days. Perhaps a study conducted for a longer duration [*e.g.,* for 72 days, as in the study by Udani *et al.* (2010)], would have allowed for a significant difference *versus* placebo to be achieved, with this dose of 4.5 g/day ResistAid™. Furthermore, given the inter-person variability, it is possible that significance would be achieved, had more subjects been enrolled in the study.

- It is noted that no significant effects, between subjects consuming ResistAid™ or placebo, were observed in antibody titers following the influenza vaccine (Udani, 2013). It is possible that arabinogalactan aids in building immunity towards bacterial infections (*e.g.,* tetanus and 23-valent pneumococcal vaccines) through an enhanced Ig response, while the effect of consumption of arabinogalactan on viral infections (*i.e.,* influenza vaccine) may be mediated through a different mechanism. The study by Riede *et al.* (2013) clearly showed a reduced incidence of common cold episodes (*i.e.,* a viral infection). A review by Dion *et al.* (2016) highlights a number of *in vitro* and *in vivo* studies that have shown the ability of arabinogalactan to activate different components of the immune system. For example, arabinogalactan has been shown to increase natural killer (NK) cells' cytotoxicity (*i.e.,* the ability to mount spontaneous cytotoxicity against tumor cells or virus-infected cells, without prior sensitization to the antigen), an action possibly mediated through an increase in interferon gamma (Hauer and Anderer, 1993).

C. Environmental Impact

An environmental impact assessment is not provided since this citizen petition relates to an action that is categorically excluded from environmental impact considerations [21 CFR § 25.32(p) – U.S. FDA, 2019a][5].

[5] 21 CFR § 25.32(p) – U.S. FDA, 2019a states the following: "Issuance, amendment, or revocation of a regulation in response to a reference amount petition as described in 101.12(h) of this chapter, a nutrient content claim petition as described in 101.69 of this chapter, a health claim petition as described in 101.70 of this chapter, or a petition pertaining to the label declaration of ingredients as described in 10.30 of this chapter."

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D. Economic Impact

In accordance with 21 CFR § 10.30, an economic impact assessment will be submitted only if requested by the Commissioner after the citizen petition has been reviewed (U.S. FDA, 2019a).

E. Certification

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

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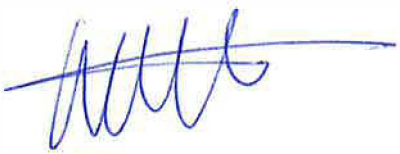

Enclosures:

Appendix A	Qualitative Results from 3 Human Studies on the Effects of Arabinogalactan on Immune Function
Appendix B	Full-Length Copies of All Relevant References

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Part	Section §	Section Title
10—Administrative practices and procedures	10.30	Citizen petition
25—Environmental impact considerations	25.32	Foods, food additives, and color additives
101—Food Labeling	101.9	Nutrition labelling of foods
	101.70	Petitions for health claims
	101.81	Health claims: Soluble fiber from certain foods and risk of coronary heart disease (CHD)

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