U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY & APPLIED NUTRITION

February 24, 2022

Aouatef Bellamine, Ph.D.
Lonza Inc.
412 Mt. Kemble Ave.
Suite 200S
Morristown, NJ 07960

Re: Docket Number FDA-2019-P-4670

Dear Dr. Bellamine:

This letter replaces our previous letter dated January 17, 2022, which was sent in error.

This letter responds to your citizen petition dated October 4, 2019, requesting that the Food and Drug Administration (FDA or we) "amend 21 CFR § 101.9(c)(6)(i)…to include arabinogalactan to the list of 'isolated or synthetic non-digestible carbohydrate(s),' based on its beneficial physiological effect on immune functioning." See Citizen Petition from Aouatef Bellamine, Lonza Inc., submitted to the Division of Dockets Management, Food and Drug Administration, dated October 4, 2019 ("Petition"), at page 1.

In accordance with 21 CFR 10.30(e)(3), we are denying your petition for the reasons stated below.

## I. FDA's Actions Regarding Dietary Fiber

In the *Federal Register* of May 27, 2016, we published a final rule entitled, "Food Labeling: Revision of the Nutrition and Supplement Facts Labels" (81 FR 33742). The final rule, among other things, defines dietary fiber 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" (see 21 CFR 101.9(c)(6)(i)). In the final rule, we identified seven isolated or synthetic non-digestible carbohydrates that have a physiological effect that is beneficial to human health. We also stated that any interested person may seek to amend the listing of added fibers through the existing citizen petition process in 21 CFR 10.30.[1]

[1] For up-to-date information on the additional non-digestible carbohydrates that FDA has determined may be added to the definition of dietary fiber, see "Questions and Answers on Dietary Fiber," available at http://www.fda.gov/food/food-labeling-nutrition/questions-and-answers-dietary-fiber#synthetic_fibers.

In the *Federal Register* of March 2, 2018 (83 FR 8997), we announced the availability of a final guidance document entitled, "Scientific Evaluation of the Evidence on the Beneficial Physiological Effects of Isolated or Synthetic Non-digestible Carbohydrates Submitted as a Citizen Petition (21 CFR 10.30)" ("final guidance"). This final guidance describes our views on the scientific evidence needed, and the typical approach for evaluating the scientific evidence, on the physiological effects of isolated or synthetic non-digestible carbohydrates added to foods that are beneficial to human health.

## II. The Petition's Requested Action

The Petition asks that we "amend 21 CFR § 101.9(c)(6)(i)…to include arabinogalactan to the list of 'isolated or synthetic non-digestible carbohydrate(s)'…" (Petition at page 1).

The Petition asserts that arabinogalactan should be added to the list of dietary fibers, as stated in 21 CFR § 101.9(c)(6)(i) "[a]s a result of the favorable and consistent effects of arabinogalactan on improved immune function" (Petition at page 1). The Petition provides the characterization of arabinogalactan, the steps the petitioner took to conduct a literature search, the results of that literature search, and summaries of the relevant human intervention studies.

The Petition includes the results of three publicly available human intervention studies to support the requested action.[2] These studies evaluated the effect of ResistAid™,[3] on the incidence of upper respiratory infections[4] or immunity following vaccinations.[5] All three human intervention studies evaluated the effects of ResistAid™, as compared to the placebo control, maltodextrin.

## III. FDA's Evaluation of the Evidence Submitted

In the final guidance, we discuss how we generally intend to evaluate publicly available studies to determine whether any scientific conclusions can be drawn regarding the physiological effect of an added non-digestible carbohydrate. In particular, we discuss the importance of being able to draw scientific conclusions about the role of the individual added non-digestible carbohydrate of interest related to the particular physiological effect being evaluated.

While evaluating publicly available studies and information, we identified other compounds (i.e., the polyphenolic flavonoids quercetin and taxifolin) present in ResistAid™, in addition to arabinogalactan, that could impact the endpoint (i.e., immune function) evaluated in the Petition

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[2] Riede L, Grube B, Gruenwald J. Larch arabinogalactan effects on reducing incidence of upper respiratory infections. *Curr Med Res Opin* 2013; 29:251-258; Udani JK. Immunomodulatory effects of ResistAid™: a randomized, double-blind, placebo-controlled, multidose study. *J Am Coll Nutr* 2013; 32:331-338; Udani JK, Singh BB, Barrett ML, Singh VJ. Proprietary arabinogalactan extract increases antibody response to the pneumonia vaccine: a randomized, double-blind, placebo-controlled, pilot study in healthy volunteers. *Nutr J* 2010; 9:32-38.

[3] According to the Petition, "Lonza Inc. manufactures arabinogalactan, 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)." See Petition at page 3.

[4] Riede *et al*. (2013).

[5] Udani (2013) and Udani *et al*. (2010).

because of their effects related to the endpoint. For example, Riede et al. 2013 identified the active ingredients in ResistAid™ as "the soluble fiber arabinogalactan and bioactive flavonoids."

In addition, a 2016 systematic review and meta-analysis on the effect of flavonoids on upper respiratory tract infections and immune function, while discussing Riede et al. 2013, identified quercetin and taxifolin as specific flavonoids contained in ResistAid™.[6] The Lonza Inc. website also confirmed the presence of these flavonoids in ResistAid™ and discussed some of their biological effects related to immune function, including information indicating that ResistAid™ "consists of arabinogalactan and bioactive flavonoids, which have antioxidant capacity" and the "polyphenolic flavonoids present in ResistAid® include taxifolin and quercetin, which have been shown to display a wide range of biochemical properties, including antioxidant and chemoprotective effects."[7]

Considerations vary for different endpoints, and some examples of these different considerations are discussed in the final guidance.[8] It is important to note that for the endpoint of immune function, a difference in the presence of flavonoids between the treatment and control is an important consideration because of the possible immune modulation effects of flavonoids. Since ResistAid™ contains flavonoids, in addition to arabinogalactan, that could impact immune function, the study outcomes could be affected unless the flavonoids are controlled for in the study design. Without controlling for these flavonoids, it is not possible to scientifically evaluate the independent physiological effect of arabinogalactan on the immune function endpoints measured in the studies. The three studies that were publicly available did not control for the presence of flavonoids in the ResistAid™ product. Because we could not evaluate the independent effect of arabinogalactan on immune function from these three studies, we had no publicly available studies from which scientific conclusions could be drawn regarding the independent effect of arabinogalactan on immune function.

## IV. Conclusion

Based on our consideration of the scientific evidence and other information submitted with the petition, as well as other pertinent scientific evidence and information, we conclude that we are unable to evaluate the effect of arabinogalactan on immune function from the publicly available studies and therefore are unable to evaluate whether the consumption of arabinogalactan has a physiological effect that is beneficial to human health. Consequently, we do not plan to propose to amend the list of nondigestible carbohydrates that meet the definition of dietary fiber to include arabinogalactan as a dietary fiber. Therefore, in accordance with 21 CFR 10.30(e)(3), we are denying your petition.

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[6] Somerville V, Braakhuis A, Hopkins W. Effect of Flavonoids on Upper Respiratory Tract Infections and Immune Function: A Systematic Review and Meta-Analysis. *Adv Nutr* 2016;7:488-97.

[7] https://www.lonza.com/products-services/consumer-health/nutrition/human-nutrition/health-ingredients/resistaid.aspx; https://www7.lonza.com/products-services/consumer-health/nutrition/human-nutrition/health-ingredients.aspx. Accessed on August 3, 2020.

[8] See final guidance at pages 9 through 11.

We recognize, of course, that new scientific information may become available related to the consumption of arabinogalactan. Although we are denying your petition, we would consider a new petition from you concerning the consumption of arabinogalactan that is based on new scientific information.

Sincerely,

Patricia A. Hansen -S

Digitally signed by Patricia A. Hansen -S
Date: 2022.02.25 12:54:24 -05'00'

***for***

Claudine Kavanaugh, Ph.D., MPH, RD
Director
Office of Nutrition
and Food Labeling
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