November 20, 2023

The Honorable Xavier Becerra
Secretary
Department of Health and Human Services
200 Independence Avenue, SW
Washington, D.C. 20201

The Honorable Robert M. Califf, MD
Commissioner of Food and Drugs
Food and Drug Administration
10903 New Hampshire Avenue
Building 32, Room 2346
Silver Spring, MD 20993

Dockets Management, FDA-2023-P-3942
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

Re: Comments on FDA Citizen Petition to Label Gluten as a Major Food Allergen
FDA Docket Number: FDA-2023-P-3942 ("Citizen Petition")

Dear Secretary Becerra and Commissioner Califf:

As an immunologist and Chief Scientific Officer of Provention Bio, I am writing to provide comments in support of Celiac Journey's FDA Citizen Petition to require the labeling of Gluten on all food packages in the United States, like Gluten is required to be declared on food labels in 87 other countries worldwide.[1]

My Background

I trained as an immunologist and have specialized in autoimmunity in general, and in the related conditions celiac disease and type 1 diabetes in particular. I earned a PhD for work on the pathophysiology and diagnosis of celiac disease, with my thesis "New immunological approaches in the diagnosis and pathogenesis of Celiac Disease and other enteropathies." I have led several entrepreneurial pursuits of diagnostic and therapeutic solutions for people living with celiac disease, including Provention Bio, which I co-founded and for which I currently serve as Chief Scientific Officer. Provention Bio, acquired by Sanofi in April 2023, was founded to develop interventions to restore immune balance, thus intercepting or preventing immune-mediated diseases. The FDA approval of teplizumab/TZIELD® in type 1 diabetes, the first-ever non-chronic immune resetting agent in T cell autoimmunity, is the culmination of 30 years of dedication to

[1] https://www.regulations.gov/document/FDA-2023-P-3942-0001

Immunology. Provention Bio, now a Sanofi Company, is also developing PRV-015 for the treatment of gluten-free diet non-responding celiac disease (NRCD), an antibody currently in Phase 2b.

Before Provention, I co-founded and was CEO and Chief Medical Officer of Celimmune, a biotech company dedicated to celiac disease and intestinal T cell lymphoma, a serious complication of long-term gluten consumption by celiac patients (entity is referred to as "refractory celiac disease type II"). Celimmune achieved proof-of-concept in both celiac disease and refractory celiac type II with AMG-714 and was acquired by Amgen in 2017.

Before Celimmune, I was Chief Medical Officer of Alba Therapeutics, the second-ever start-up biotech company in the celiac disease space, which took a molecule to Phase 2b (unfortunately unsuccessful).

Throughout my career, I have authored or co-authored over 100 peer-reviewed articles, book chapters and patents, and I have led R&D projects and teams in diverse settings from start-ups to Big Pharma and am fluent in all phases of drug development. I have been fortunate to have led or participated in the development of several FDA-approved products: Provention's teplizumab/TZIELD®, Astra Zeneca's benralizumab/FASENRA®; Bristol Myers-Squibb's abatacept/ORENCIA®, and belatacept/NULOJIX®; and Janssen/Johnson & Johnson's ustekinumab/STELARA® and guselkumab/TREMFYA®.

In addition to my therapeutic focus, I also co-founded a diagnostics company called Glutenostics, which commercializes products to detect gluten in the diet. This company was created out of the realization that gluten contaminates most of American prepared foods and patients need more tools to detect contaminating gluten.

For all my work in the space, I was honored to receive the inaugural Impact Award from Beyond Celiac this year. Mrs. Alice Bast, CEO of Beyond Celiac, the largest patient advocacy group, said:

> "Throughout his extensive career, Dr. Leon has demonstrated a life-long commitment and passion for celiac disease research, sharing the Beyond Celiac vision of a world in which people with celiac disease can eat without fear. With a passion for translational research, innovation and disruptive ideas, Dr. Leon has led a number of successful entrepreneurial pursuits, serving as the co-founder of Glutenostics, the Chief Scientific Officer and co-founder of Provention Bio, and previously co-founding and serving as the Chief Executive Officer and Chief Medical Officer of Celimmune, as well as the Chief Medical Officer of Alba Therapeutics - four companies all developing solutions for people living with celiac disease."[2]

[2] https://eveningbeyond23.funraise.org/

Food is Medicine – Label Gluten to Protect People Living with Celiac Disease

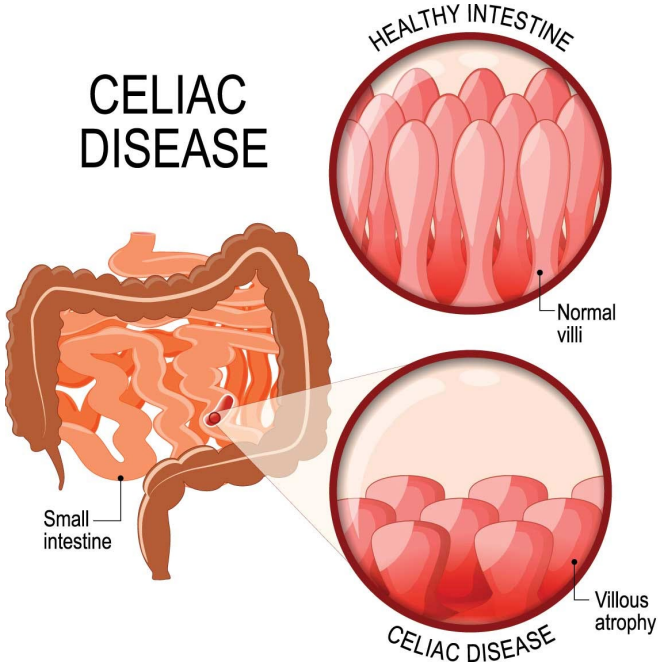
I agree with the FDA that people with Celiac Disease "face potentially life-threatening illnesses if they eat gluten, typically found in breads, cakes, cereals, pastas, and many other foods… There is no cure for celiac disease and the only way to manage the disease is to avoid eating gluten."[3]

However, research has shown that 44% of people with Celiac Disease who follow a strict Gluten Free diet still get "glutened" (i.e., consume sufficient inadvertent gluten to trigger immune activation) once a month, and "many with celiac disease pay over 40% more in annual healthcare costs."[4]

While I remain hopeful and continue striving to develop pharmacological treatments for Celiac Disease, the fact is that the only available treatment today is a completely strict Gluten Free diet for life. As little as 10 mg of gluten per day can cause immune activation, and that is why we need the FDA to require the labeling of Gluten so patients can best avoid it.

To better understand the serious adverse health reactions that Gluten ingestion can cause, it is instructive to visualize villous atrophy that occurs in celiac patients.

Visualizing Villous Atrophy: Gluten Triggered Auto-Immune Cascade in Celiac Patients Damages the Small Intestine



[3] https://www.fda.gov/consumers/consumer-updates/gluten-free-means-what-it-says
[4] https://twitter.com/abast/status/1551780196243603457 and https://www.beyondceliac.org/

According to the NIH's "Notice of Special Interest (NOSI): Accelerating Progress in Celiac Disease Research" that was published on November 23, 2021, there are more than 3 million Americans who have Celiac Disease.

> "Celiac disease is an autoimmune disease that occurs in genetically susceptible individuals who develop an immune response to ingested gluten. This disease affects greater than 1% of the US population, and incidence appears to have been increasing over the last several decades. The only known treatment is life-long strict avoidance of all forms of wheat, rye, and barley. Although a gluten-free diet is an effective treatment in many individuals, recent research has revealed that up to 50% of individuals following a gluten-free diet are inadvertently exposed to gluten, and a substantial minority develop persistent or recurrent symptoms.
>
> Clinical manifestations are multifaceted and include gastrointestinal (ranging from severe malabsorption to subclinical damage of the gastrointestinal tract) as well as extraintestinal (e.g., skin) expressions of disease. Additional manifestations may vary from subclinical damage of the gastrointestinal tract to refractory celiac disease that is non-responsive to a gluten-free diet. Although rare, celiac disease is associated with increased risk of gastrointestinal tract cancers and lymphomas."[5]

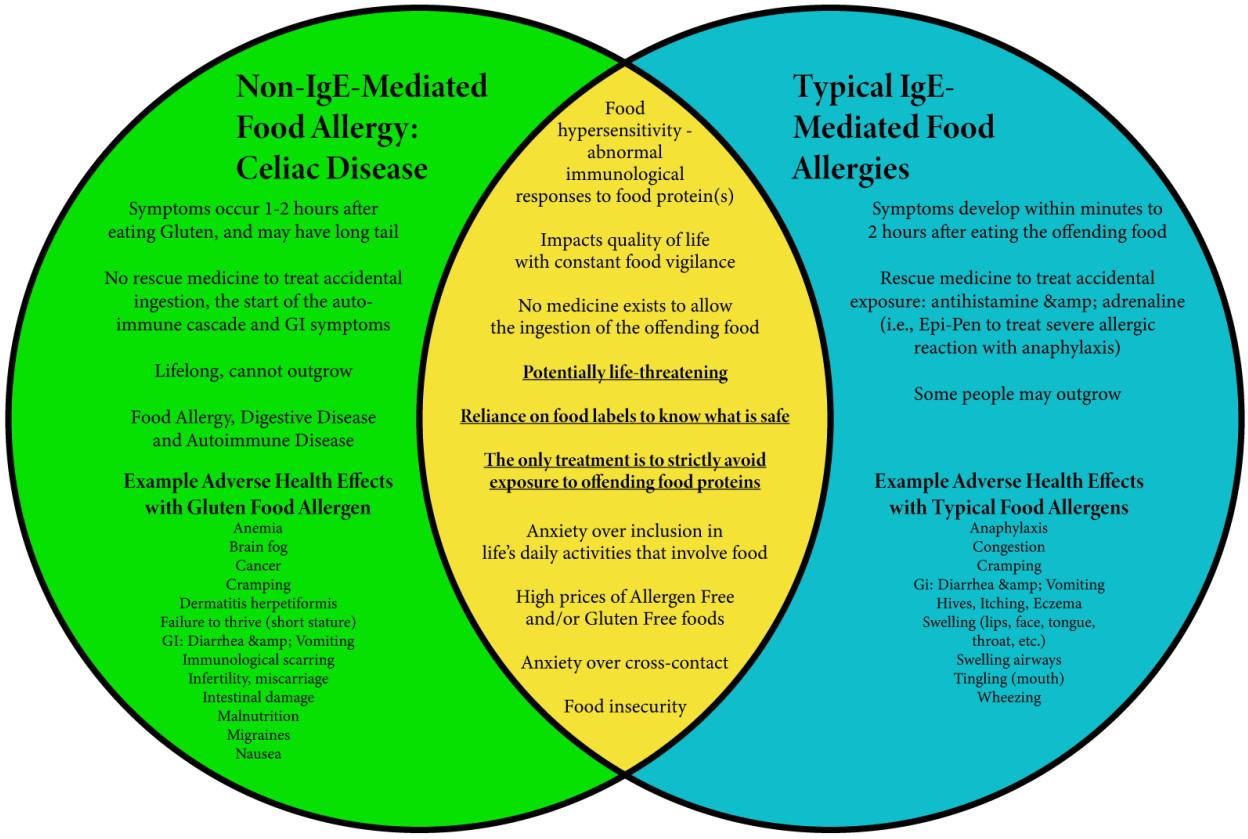
For someone with Celiac Disease, eating, sleeping, thinking, learning and working are major life activities that can be impacted on a daily basis through the ingestion of Gluten, and there are various bodily systems which can be impacted including: gastrointestinal (digestive), nervous (anxiety, ataxia and neuropathy), skeletal, reproductive (infertility) and integumentary. Celiac patients are also at a greater risk of being diagnosed with additional auto-immune disorders.

Gluten, the main protein of wheat, barley and rye, is a peculiar dietary component because humans have no glutenases - and gluten is generally digested and/or excreted. Gluten is enriched in food and used as additive for its 'binding' properties, providing consistency to diverse foods. However, in people with genetic susceptibility for immune disease, gluten can cause three different diseases: 1) IgE-mediated allergy, 2) IgG-mediated gluten intolerance (up to 10% of the population), and 3) T cell-mediated autoimmune disease (i.e., celiac disease, with its characteristic IgA production, 1% of the population and growing). People affected by any of these extremely common diseases need to be able to avoid gluten, hence food labelling is essential.

The diagram below illustrates the key near-peer similarities between food allergies that are Non-IgE-Mediated Mechanisms with Celiac Disease (Gluten) and typical IgE-Mediated Mechanisms: potentially life-threatening, the only treatment is to strictly avoid the food allergen(s), and consumers' reliance on food labels to know what is safe to eat.

[5] https://grants.nih.gov/grants/guide/notice-files/NOT-AI-22-004.html

The Similarities and Differences Between Non-IgE-Mediated Mechanisms with Celiac Disease & Typical IgE-Mediated Mechanisms



Labeling Gluten as a Major Food Allergen is congruent with the conclusions of international food safety authorities and expert committees comprised of scientists, regulators, physicians, clinicians and risk managers from academia, government and the food industry including:

- 1999 Joint Food and Agriculture Organization of the United Nations/World Health Organization Expert Committee on Food Additives "Evaluation of Certain Food Additives and Contaminants: Fifty-third Report of the Joint FAO/WHO Expert Committee on Food Additives. 2000. WHO Technical Report Series 896. World Health Organization, Geneva ("1999 FAO-WHO Expert Consultation"; also referred to as the "1999 Codex criteria).[6]
- 2021 Food and Agriculture Organization of the United Nations/World Health Organization Expert Consultation on Risk Assessment of Food Allergens, which included the FDA's Dr. Lauren Jackson, Chair, and the FDA's Dr. Stefano Luccioli ("2021 FAO/WHO Expert Consultation"). The 2021 FAO/WHO Expert Consultation found, "[b]ased on systematic and thorough assessments which used all three criteria (prevalence, severity and potency), the Committee recommended that the following should be listed as priority allergens: Cereals containing gluten (i.e., wheat and other Triticum species, rye and other Secale species, barley and other Hordeum species and

[6] https://apps.who.int/iris/bitstream/handle/10665/42378/WHO_TRS_896.pdf

their hybridized strains), crustacea, eggs, fish, milk, peanuts, sesame, specific tree nuts (almond, cashew, hazelnut, pecan, pistachio and walnut)." [7]

In addition to being naturally present in wheat, barley and rye products, gluten also often contaminates oats manufactured in the same facilities. According to research cited in the FAO and WHO 2022 Risk Assessment of Food Allergens, Part 1 - Review and validation of Codex Alimentarius Priority Allergen List Through Risk Assessment. Meeting Report, Food Safety and Quality Series No. 14, Rome,

> "It might be considered that oats should be on a regional priority allergen list because oats are generally contaminated, and often at significant levels, with gluten containing cereals. In Canada, taking into consideration lot-to-lot variability, approximately 88 percent of commercial oats samples (n = 133) were reported to be contaminated above the Codex-recommended gluten-free level (20 ppm), gluten concentration ranging from 21 to 3800 mg/kg of oats (Koerner et al., 2011). If oats are not on a priority allergen list, the possible presence of (contaminated) oats as an ingredient remains, and several products may cause reactions in consumers with coeliac disease. For this reason, oats are included in Canadian legislation."[8]

Requested Action

Today, Wheat is required to be labeled in the U.S., but Gluten is not. Gluten is found in Wheat, Barley, Rye and most Oats. This Citizen Petition is requesting a long-overdue reckoning by the FDA to better protect more than 3.3 million Americans with Celiac by labeling Gluten (Wheat, Barley, Rye and Oats) as a Major Food Allergen on all packaged foods. Under its existing authority in the Food Allergen Labeling and Consumer Protection Act in statute at 21 U.S.C. § 343(x), we request that the FDA issue a rule to: 1) require that all ingredients with Gluten be listed by name in the ingredient lists of all foods and; 2) add Gluten to the FDA's list of allergens in Sec. 555.250 of its Compliance Policy Guides Manual, "Statement of Policy for Labeling and Preventing Cross-contact of Common Food Allergens" to address both labeling and cross contact issues related to food manufacturing practices.

The global implementation of the 1999 Codex Criteria and the 2021 FAO-WHO Expert Consultation can be seen in how 87 countries worldwide require that Gluten be labeled on all packaged foods, according to the map and chart produced by the Food Allergy Research and Resource Program at the University of Nebraska-Lincoln.[9]

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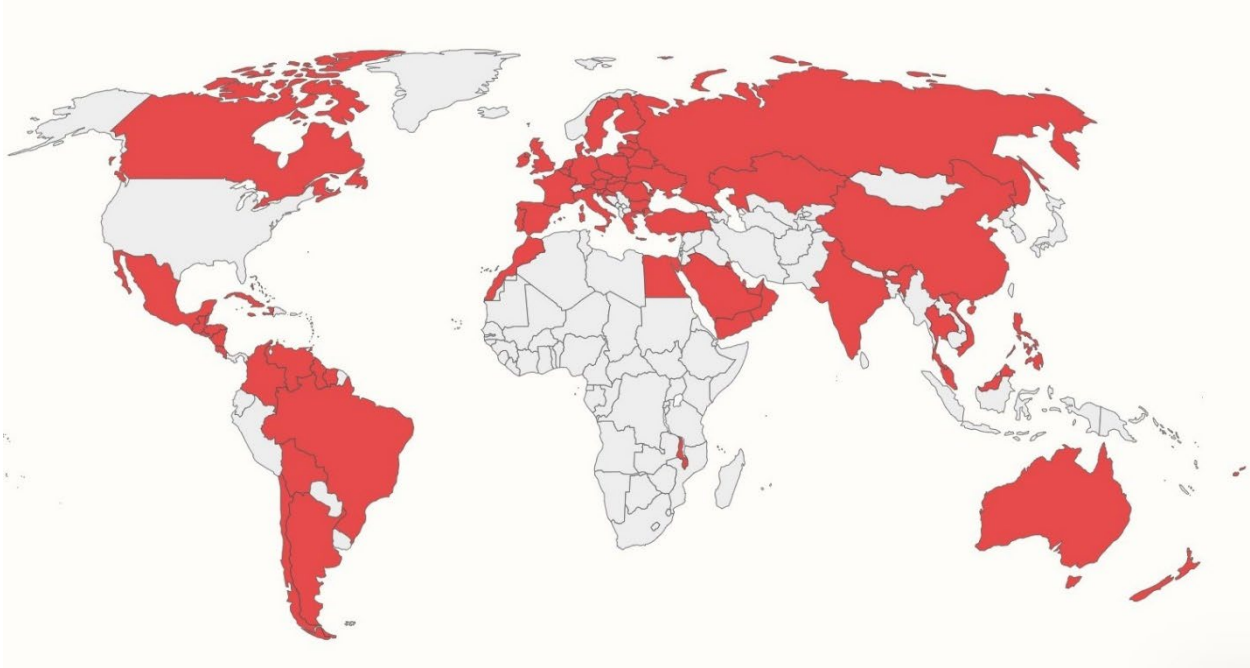
[7] http://www.fao.org/3/cb4653en/cb4653en.pdf

[8] https://www.fao.org/3/cb9070en/cb9070en.pdf , and https://www.tandfonline.com/doi/pdf/10.1080/19440049.2011.579626?

[9] https://farrp.unl.edu/IRChart



Importantly, unlike food allergies with IgE-Mediated mechanisms, there is no rescue medicine (i.e., adrenaline or antihistamine) to treat accidental ingestion of Gluten and the start of the auto-immune cascade in food allergy with Non-IgE-Mediated mechanisms such as Celiac Disease. Additionally, those with a Non-IgE-Mediated food allergy to Gluten cannot outgrow their food allergy – Celiac is lifelong (until such time as a cure may be developed).

While U.S. consumers' reactions to a top 9 Major Food Allergens and Gluten vary, their consumer habits are the same -- they avoid purchasing foods that contain the allergen(s) that cause a potentially life-threatening immunological adverse reaction.

However, the key difference from a consumer protection standpoint is that under the Food Allergen Labeling and Consumer Protection Act of 2004 ("FALCPA"), the labeling scheme for the top 9 Major Food Allergens in the U.S. is mandatory, but the labeling of Gluten is permissive. Just because something is Wheat free does not mean its Gluten Free. In other words, whereas sufferers of the current top 9 Major Food Allergens in the U.S. rely on what ingredients are expressly included in required labeling disclosures of packaged foods, the Celiac community cannot rely on manufacturers to declare Gluten on food labels.

I agree with the comments from Dr. Virginia Stallings, a board-certified nutrition pediatrician, Professor of Pediatrics and Director of the Nutrition Center at the Children's Hospital of Philadelphia. Dr. Stallings was also the Editor and Chair of the National Academies of Sciences, Engineering, and Medicine, Committee on Food Allergies which published the seminal work: "Finding a Path to Safety in Food Allergy: Assessment of

the Global Burden, Causes, Prevention, Management and Public Policy." As it pertains to Gluten, Dr. Stallings opined:

> "While a Non-IgE-Mediated food allergy does not trigger anaphylaxis and is not immediately life-threatening, people with Celiac Disease face potentially life-threatening and severe adverse health effects that can arise through gluten ingestion including by way of example and not limited to: anemia, cancer, heart disease, immunological scarring, intestinal damage and malnutrition… A gluten free diet is not all that is needed to treat Celiac Disease; rather a gluten free diet is all that has ever been historically available to treat Celiac Disease. Additionally, with respect to labeling food products in the United States, the voluntary gluten free labeling scheme does not sufficiently protect consumers who are on medically required and very restrictive gluten free diets. My strong recommendation is that gluten be labeled on all packaged foods in the United States, in accordance with the 2021 FAO/WHO Expert Consultation, just like it is in more than 85 countries around the world."[10]

I am respectfully requesting that the FDA change the voluntary labeling rule to a mandatory labeling rule to keep 3.3 million Americans with Celiac safer. I would be pleased to answer any questions that you may have. Thank you.

Sincerely,

Francisco Leon, MD, PhD

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[10] https://downloads.regulations.gov/FDA-2021-N-0553-1169/attachment_1.pdf