COMMONWEALTH OF VIRGINIA
Meeting of DHP and Board of Pharmacy

Perimeter Center, 9960 Mayland Drive, 2nd Floor
Henrico, Virginia 23233

Tentative Agenda of Work Group Regarding Medication Labeling (HB 831)
September 14, 2026
2 PM

TOPIC

Call to Order of Meeting: David Brown, DC, Director, DHP

- Welcome & Introductions
- Approval of Agenda

Call for Public Comment: The work group will receive public comment at this time. The work group will not receive comment on any board regulation process for which a public comment period has closed, or any pending disciplinary matters associated with a board.

Topics:

- Review of the charge of the work group
- Review background materials within agenda packet
    - Letter from Speaker Don Scott requesting review - 2
    - Information from FDA Website regarding medication and gluten - 3-5
    - *Gluten in Drug Products and Associated Labeling Recommendations Guidance for Industry* - 6-22
    - FDA Response to 2015 petition - 23-58
    - FDA Medwatch Voluntary Reporting Form - 59-62
    - H.R. 3821, 119TH Congress 1st Session - 63-65
- Discussion
- Next steps

Adjourn

COMMONWEALTH OF VIRGINIA

HOUSE OF DELEGATES
RICHMOND

DON SCOTT
SPEAKER
SPEAKER'S ROOM
STATE CAPITOL
POST OFFICE BOX 406
RICHMOND, VIRGINIA 23218
EIGHTY-EIGHTH DISTRICT

COMMITTEE ASSIGNMENTS:
RULES (CHAIR)

May 27, 2026

David Brown, D.C., Director
Department of Health Professions

Caroline Juran, Executive Director
Board of Pharmacy

9960 Mayland Drive, Suite 300
Richmond, VA 23233-1463

VIA ELECTRONIC MAIL

Dear Director Brown and Ms. Juran:

During the 2026 General Assembly Session, the House Committee on Rules considered a bill that was ultimately recommended for further study by the Department of Health Professions and the Board of Pharmacy. With respect to the Department and Board's existing workload and resources, I request the Department and Board, in coordination with relevant stakeholders, undertake the following:

- **House Bill 831 –** Review regulations related to ingredient labeling of medications, drugs, and vaccines sold and distributed in the Commonwealth, with particular focus on assessing the feasibility of requiring labeling for products that contain gluten, whether as an active or inactive ingredient.

Please do not hesitate to contact my office if you have any questions or require additional information.
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Sincerely,

Don Scott

DS/krn

cc: The Honorable Hillary Pugh Kent
Cathy Hooe

Medications and Gluten

The majority of orally administered drug products either contain no gluten or virtually no gluten. FDA has issued a draft guidance on *Gluten in Drug Products and Associated Labeling Recommendations* (/media/116958/download). The draft guidance provides recommendations on how certain oral drug products should be labeled regarding gluten, a matter of interest to individuals with celiac disease.

The draft guidance gives drug manufacturers a recommended statement to include in their labeling when truthful and properly supported: “Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).” The draft guidance also describes where to place that statement in the product labeling.

The draft guidance encourages drug manufacturers to have accurate information about their products' gluten content available so they can respond to questions from consumers and health care professionals. Some individuals with celiac disease have faced difficulty when trying to determine whether specific drug products contain gluten. The recommendations contained in FDA’s draft guidance are intended to reduce this uncertainty and to provide information to consumers and healthcare professionals regarding gluten in drug products.

This draft guidance was developed with individuals with celiac disease in mind. However, the recommendations in this draft guidance may be of interest to individuals with other with other conditions that are treated with a gluten-free diet.

The following Questions & Answers provide additional information for consumers with questions about gluten in drug products:

Questions and Answers about Gluten and Oral Drug Products

What is gluten?

FDA uses the term “gluten” in its guidance on oral drug products as meaning certain proteins found in wheat, barley, and rye or their crossbred hybrids that lead to symptoms associated with celiac disease.

What is celiac disease?

Celiac disease (also known as celiac sprue) is an immune-based reaction to dietary gluten that primarily affects the small intestine in susceptible individuals; unmanaged celiac disease can lead to serious health complications. Approximately 1 percent of the U.S. population has celiac disease. It is characterized by ongoing inflammation of part of the lining of the small intestine that generally heals if foods containing gluten are excluded from the diet and returns if they are reintroduced. At this time, the treatment for celiac disease is adherence to a gluten-free diet. Information is available on FDA's food-labeling regulations and gluten-free diets (/food/allergens/gluten-free-labeling-foods) web page.

What types of ingredients that may contain gluten are in oral drug products?

The majority of oral drug products either contain no gluten or virtually no gluten.

Based on information available to the Agency, we are aware of no oral drug products currently marketed in the United States that contain wheat gluten or wheat flour intentionally added as an inactive ingredient. We would expect any such product, if it existed, to include wheat gluten or wheat flour in the list of ingredients in its labeling.

FDA has identified very few oral drugs that contain wheat starch as an ingredient. Starch can also be used as a starting material for manufacturing various ingredients found in oral drugs. Starch used for this purpose is often corn starch or potato starch, not wheat starch. Even if wheat starch were used, either as an ingredient or as a starting material, there would be very little gluten, if any, expected to be present in the ingredient or the drug product. Very few, if any, oral drug products contain ingredients derived from barley or rye.

Typically, how much gluten is in a drug product?

The vast majority of oral drug products either contain no gluten or virtually no gluten. In the very rare cases where gluten may be present, we estimate based on drug formulation information that wheat starch and other ingredients derived from wheat would contribute no more than 0.5 mg gluten to a unit dose of an oral drug product. This amount is less than may be found in a single 30-gram serving of food labeled gluten-free according to FDA's regulations.

How do I find out what ingredients my drug product contains?

For nonprescription drug products, ingredients are listed on the "Drug Facts" label in the "inactive ingredients" section. For prescription drug products, ingredients will generally be listed on the labeling in the "Description" section.

You can also look up the labeling for more than 90,000 prescription and nonprescription drug products on the internet at DailyMed (http://dailymed.nlm.nih.gov/dailymed). Here are a couple of points to keep in mind when looking up information about a drug product:

- Be sure that the product label you are looking at matches the product you are interested in getting more information about. For example, the product name and product manufacturer or distributor listed on the label should match the product you are interested in.
- If the list of ingredients does not mention wheat gluten or wheat flour, then the product should not contain gluten in an amount that would harm a typical (non-refractory) individual with celiac disease.

FDA encourages drug manufacturers to have accurate information on the sources of their ingredients available so they can respond to questions from the public and health care providers.

Related Information

- Gluten in Drug Products and Associated Labeling Recommendations; Draft Guidance for Industry (/media/116958/download)
- Report a problem to MedWatch, the FDA Safety Information and Adverse Event Reporting Program (/medwatch-fda-safety-information-and-adverse-event-reporting-program)
- Citizen Petition and Response from FDA, 2017 (https://www.regulations.gov/docket?D=FDA-2015-P-5081)
- Citizen Petition and Response from FDA, 2015 (https://www.regulations.gov/docket?D=FDA-2008-P-0333)
- Gluten in Drug Products, Request for Information (RFI), Docket No. FDA-2011-N-0842-0001) issued 12-21-11, closed for comments 3-20-12 (http://www.regulations.gov/#!documentDetail;D=FDA-2011-N-0842-0001)
- Celiac Disease Awareness Campaign of the National Institutes of Health (NIH) (http://www.celiac.nih.gov/)

Gluten in Foods

- Gluten and Food Labeling (/food/allergens/gluten-free-labeling-foods)

Gluten in Drug Products and Associated Labeling Recommendations

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Marci Kiester 301-796-0600, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2017
Labeling

Gluten in Drug Products and Associated Labeling Recommendations

Guidance for Industry

Additional copies are available from:
Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353
Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm
and/or
Office of Communication, Outreach and Development
Center for Biologics Evaluation and Research
Food and Drug Administration
10903 New Hampshire Ave., Bldg. 71, Room 3128
Silver Spring, MD 20993-0002
Phone: 800-835-4709 or 240-402-8010
Email: ocod@fda.hhs.gov
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

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Labeling

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Gluten in Drug Products and Associated Labeling Recommendations
Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to convey to drug manufacturers FDA's recommendations on how certain drug products should be labeled regarding gluten, a matter of interest to individuals with celiac disease. Some individuals with celiac disease have faced difficulty when trying to determine whether specific drug products contain gluten. Confronted by uncertainty, some patients may forego important medication rather than risk an adverse reaction to gluten. Thus, even if gluten is not present at levels that would harm a typical individual with celiac disease, that individual may be harmed through uncertainty and lack of information.

Celiac disease (also known as celiac sprue) is an immune-based reaction to dietary gluten that primarily affects the small intestine in susceptible individuals; unmanaged celiac disease can lead to serious health complications. Approximately 1 percent of the U.S. population has celiac disease (Binder 2015). It is characterized by ongoing inflammation of part of the lining of the small intestine that generally heals if foods containing gluten are excluded from the diet and returns if they are reintroduced. At this time, the treatment for celiac disease is adherence to a gluten-free diet.

FDA's food labeling regulations define *gluten* as "proteins that naturally occur in [wheat, barley, and rye or their crossbred hybrids] and that may cause adverse health effects in persons with celiac disease (e.g., prolamins and glutelins)" (21 CFR 101.91(a)). Consistent with this definition, the term *gluten* in this document refers to certain proteins found in wheat, barley, and rye or their crossbred hybrids that lead to symptoms associated with celiac disease.

This guidance pertains to human drug products that pass through the small intestine:

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

- Orally ingested drug products.[2]

- Topical drug products applied to or near the lips (e.g., lip sunscreens).[3]

- Drug products applied inside the mouth (e.g., cold sore treatments, drugs delivered to or via the oral cavity).

In this guidance, *oral drug product* refers to this group of products. Gluten is not believed to harm individuals with celiac disease through routes of exposure other than oral or enteral ingestion.

This guidance was developed with celiac disease in mind. However, the recommendations in this guidance may be of interest to patients with other conditions that are treated with a gluten-free diet.

This guidance does not apply to food (including dietary supplements) or products regulated solely as cosmetics.[4] In addition, this guidance does not discuss labeling recommendations regarding wheat hypersensitivity.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DISCUSSION

A. Possible Sources and Amounts of Gluten in Oral Drug Products

Wheat is not used to a significant extent in the production of drug ingredients, and barley and rye are used either rarely or not at all.

1. Wheat Gluten as an Ingredient

Wheat gluten itself is never or very rarely added as an inactive ingredient to oral drug products during manufacture.[5] As discussed in section II.B of this guidance, any oral drug product that

[2] The term *drug products* includes drugs subject to licensing as biological products.

[3] This includes topical drug products that are also cosmetics, such as lipsticks that are also sunscreens.

[4] For regulations pertaining to "gluten-free" labeling of foods, see 21 CFR 101.91.

[5] In this guidance, when we say *added as an ingredient*, we are referring to the intentional and purposeful addition of that ingredient. We are not referring to the introduction of wheat gluten, for example, as an unintended contaminant or impurity associated with an ingredient. Based on information available to us during our analyses for this guidance, we are aware of no oral drug products currently marketed in the United States that contain wheat gluten intentionally added as an inactive ingredient.

contains wheat gluten as an intentionally added ingredient should be labeled to indicate its presence.

Although the use of wheat gluten as an inactive ingredient in drug products does not generally mean that the product will fail to satisfy applicable requirements for safety, we may question the addition of wheat gluten to certain oral drug products on a case-by-case basis. We would be more likely to question the use of wheat gluten as an ingredient in an oral drug product for which few or no alternative treatments are available. We would also be more likely to question its use as an ingredient in an oral drug product intended for long-term administration or intended to treat comorbidities of celiac disease.

The level at which wheat gluten would be present in an oral drug product—if added as an ingredient—is directly controlled by the drug manufacturer. In the absence of more detailed information regarding wheat gluten amounts, individuals with celiac disease may choose to avoid oral drug products that are labeled as containing wheat gluten as an ingredient.

2. Wheat Gluten as an Impurity in Ingredients Derived From Wheat

Apart from its possible addition to oral drug products as an inactive ingredient—something that rarely, if ever, occurs—wheat gluten may be present at low levels as an impurity in ingredients that are derived from wheat, such as wheat starch.

In this section, we identify drug ingredients and categories of ingredients derived or potentially derived from wheat, and we estimate how much gluten they may contribute to a unit dose of an oral drug product. In general, the quantities we estimate to be present are low and do not exceed the amounts of gluten that could be found in food products labeled gluten-free under FDA's regulations (21 CFR 101.91). We present this analysis because (1) it has informed our thinking about regulatory options associated with gluten in oral drug products, (2) we would like drug manufacturers to consider the information in this section and review the ingredients they use in their drug products, and (3) if the information or assumptions underlying our analysis are proven incorrect, we would reconsider available regulatory options.

Drug manufacturers are in the best position to review their specific formulations for oral drug products and to question their ingredient suppliers about ingredients potentially derived from wheat, purification methods, and analytical testing results. We urge manufacturers to consider gluten content when formulating products using ingredients potentially derived from wheat or wheat starch.

a. Wheat flour

We are aware that some manufacturers have reported the direct addition of wheat flour to oral drug products in the past—but only very rarely. We are not aware of an oral drug product currently being marketed in the United States that contains wheat flour as an ingredient. As discussed in section II.B of this guidance, any oral drug product that contains wheat flour as an intentionally added ingredient should be labeled to indicate its presence.

The total protein content of wheat flour is generally 13 percent, with gluten representing part of the total protein.[6] The amount of gluten present in an oral drug product to which wheat flour has been added as an ingredient would depend on how much wheat flour is used. Because use of wheat flour in any drug product is so rare, we do not have good information regarding upper, lower, and typical levels that would be present in a drug product. We believe individuals with celiac disease might choose to avoid oral drug products that are labeled as containing wheat flour in the absence of more detailed information about the drug product's gluten content.

b. Wheat starch

As with wheat gluten and wheat flour, we believe wheat starch is added to oral drug products as an ingredient only very rarely. Other sources of starch (e.g., corn, potato) are more commonly used in pharmaceutical products. As discussed in section II.B of this guidance, any oral drug product that contains wheat starch as an intentionally added ingredient should be labeled to indicate its presence.

A monograph for wheat starch in the National Formulary (NF) includes a 0.3 percent limit on total protein but does not include a limit on gluten content.[7] The gluten content will be some proportion of the total protein content. Based on published information, we understand the gluten content of wheat starch suitable for use in drug products is variable but is typically in the range of 100 to 500 mg/kg (see, e.g., Kasarda, Dupont, et al. 2008). Based on our review of drug formulation information, we expect wheat starch—in the rare cases in which it is used in oral drug products—to contribute less than 0.1 mg gluten to a unit dose of an oral drug product.

c. Ingredients derived from starch

Starch is used as a starting material for manufacturing various ingredients added to oral drug products. The starch used for this purpose is often corn or potato starch, not wheat starch. Nevertheless, we recognize that very small amounts of wheat gluten may be present in starch-derived ingredients if wheat starch is used as the starting material.

Ingredients in this category—*potentially* derived from wheat starch—include modified starch, pregelatinized starch, and sodium starch glycolate. This category also includes starch hydrolysates (e.g., maltodextrin, dextrates, dextrose, maltose, and sugar alcohols such as sorbitol, xylitol, maltitol, and mannitol) and hydrogenated starch hydrolysates (mixtures of sugar alcohols).

As with wheat starch, compendial monographs for these ingredients do not include specific limits on gluten content. We have found published reports regarding the gluten content for only a limited number of ingredients derived from wheat starch. In the absence of such specific information, we have made the conservative assumption that wheat-derived modified starches

[6] According to the International Starch Institute, the typical value of total protein in wheat flour on a dry matter basis is 13 percent. See the Institute's Technical Memorandum on Wheat Starch, available at http://www.starch.dk/isi/starch/tm33wheat.asp, accessed August 2017.

[7] NF 35 Monograph: Wheat Starch, current at the time of this publication.

(e.g., modified starch, pregelatinized starch, sodium starch glycolate), although more highly processed than wheat starch, might contain gluten at the same concentrations at which gluten might be found in wheat starch: 100–500 mg/kg. Based on published literature, we believe that starch hydrolysates and hydrogenated starch hydrolysates derived from wheat may contain up to 40 mg/kg gluten (European Food Safety Authority 2007). Based on drug formulation information, we estimate that these ingredients may contribute less than 0.5 mg gluten to a unit dose of an oral drug product.

d. Ingredients produced through fermentation

Some ingredients, including citric acid and ethanol, may be produced by fermentation, in which microorganisms feed on carbohydrates from plant sources that potentially include wheat. See, for example, 21 CFR 184.1033, which describes the production of food-grade citric acid by various methods, including fermentation. If the fermentation medium includes wheat or wheat-derived ingredients, an ingredient produced by fermentation may—depending on how it is purified—contain small amounts of gluten. Compendial monographs for these ingredients do not include gluten limits.

In some cases, an ingredient such as ethanol[8] may be purified through distillation. It is unlikely that gluten (or any protein) would be present in ethanol purified by distillation using good manufacturing practices, considering the high volatility of ethanol compared with the much lower volatility of a large molecule such as gluten.

In other cases, the ingredient is highly purified through other means. Anhydrous citric acid, USP, for example, is not less than 99.5 percent pure. We expect the presence of any residual gluten in such ingredients to be very low. Based on drug formulation information we have reviewed, we expect ingredients produced through fermentation to contribute no more than 0.5 mg gluten to a unit dose of an oral drug product.

As with all of our estimates presented above, there is some uncertainty surrounding the amount of gluten that may be present in drug ingredients produced through fermentation. A more certain estimate would require production information or analytical test results covering multiple batches of the full range of ingredients made by producers around the world. In the absence of such information, we have relied on total protein limits in compendial monographs and published reports covering certain ingredients.

e. Wheat germ oil

We are aware that wheat germ oil[9] may be used as an ingredient in certain products applied topically to the lips or skin, such as lip balms or sunscreen products. If the wheat germ oil is highly refined, it is unlikely to contain detectable amounts of gluten. Even if the oil is not highly

[8] Alcohol, USP. (USP=United States Pharmacopeia.)

[9] Sometimes identified as *Triticum vulgare* (wheat) germ oil.

refined, we believe the presence of any gluten in a product applied topically to the lips would be very low, and any oral ingestion of gluten associated with the product would be insignificant.

3. Wheat Gluten as an Adventitious Contaminant

In theory, wheat gluten that is not associated with a wheat-derived ingredient could be introduced into an oral drug product as an adventitious contaminant (e.g., as a result of contact with gluten during manufacture, processing, transportation, or storage). Although we do not have systematic data in this area, we expect that any gluten present adventitiously in oral drug products would be present only in very small amounts. In all likelihood, the amount of gluten would be below the limits of detection associated with current analytical test methods. It is also likely that the amount of gluten would be well below the levels we have estimated an inactive ingredient, such as wheat starch, could potentially contribute to an oral drug product. Current good manufacturing practice (CGMP) regulations for drug products reflect a basic obligation to prevent contamination of a drug being processed,[10] and a violation of the CGMP regulations can result in an enforcement action. FDA would consider taking action if an oral drug product were found to contain significant amounts of gluten as a contaminant.

B. Labeling

If a drug included an ingredient derived from wheat, barley, or rye, the ingredient would most likely be wheat-derived. The amount of gluten potentially contributed by a wheat-derived ingredient to a unit dose of an oral drug product (unless that ingredient is wheat gluten itself or wheat flour) is expected to be less than 0.5 mg, as a high estimate.[11] As discussed in section II.A of this guidance, most oral drug products are not expected to contain ingredients derived from wheat, barley, or rye. The likelihood of them including more than one such ingredient is even less. Thus, it is expected that the amount of gluten potentially present in a unit dose of an oral drug product is less than the amount of gluten that could potentially be found in a single serving of a cookie (30 grams) labeled *gluten-free* in accordance with FDA's regulations at 21 CFR 101.91 (if all of the criteria of that regulation are satisfied).[12] Moreover, the amount of gluten estimated to be potentially present in a unit dose of an oral drug product (less than 0.5 mg) is significantly less than the range at which gluten is estimated to be present in a gluten-free diet (5 to 50 mg) (La Vieille, Dubois, et al. 2014; Catassi, Fabiani, et al. 2007).[13] This leads FDA to conclude that individuals who respond well to a gluten-free diet are at low risk of experiencing problems as a result of the possible presence of gluten in a drug product. However, we expect

[10] See generally Current Good Manufacturing Practice for Finished Pharmaceuticals, 21 CFR part 211.

[11] Our estimate is based on assumptions regarding gluten content and ingredient usage that favor a high estimate (i.e., we considered high levels of use for each inactive ingredient potentially derived from wheat, and we considered the high end of the range at which gluten is reasonably expected to be present in each ingredient).

[12] A 30-gram serving of food, corresponding to a single cookie, for example, could contain up to 0.6 mg gluten while bearing a gluten-free statement if the criteria for the definition of *gluten-free* are satisfied. 30 grams x 20 ppm=0.6 mg. See reference amounts customarily consumed per eating occasion in FDA's food labeling regulations, 21 CFR 101.12, Table 2.

[13] We recognize that gluten-free diets may be highly variable, and individuals diagnosed with refractory celiac disease may have more restrictive diets.

that they might choose to avoid using oral drug products labeled as containing *wheat gluten* or *wheat flour* as an ingredient in the absence of more information about the product's actual gluten content.

We have also considered the potential impact on those individuals with celiac disease who take multiple oral medications each day. Considering that inactive ingredients are typically derived from sources other than wheat, and that 0.5 mg of gluten per unit dose is a high estimate for gluten in an oral drug product, we expect that an individual taking multiple drug products per day would ingest much less gluten, if any, from drugs than an individual with celiac disease adhering to a gluten-free diet may ingest from food.

Some celiac patients are more sensitive to gluten than others and do not respond well to a gluten-free diet.[14] Patients who are more sensitive to gluten will likely seek to eliminate all sources of ingested gluten, or at least minimize exposure as much as possible. In all probability, these patients are under specialized care and would avoid those rare oral drug products containing added wheat starch in addition to those containing added wheat gluten or wheat flour. Additionally, they or their caregivers would likely reach out to physicians, pharmacists, other health care providers, or drug manufacturers for information about possible inclusion of wheat-derived ingredients in their oral drug products. We encourage drug manufacturers to have accurate information on the sources of their ingredients available so they can respond to questions from the public and health care providers.

1. Ingredient Labeling: Current Regulations and Practice

As described below, drug ingredients are generally identified in labeling, but substances that are present merely as impurities generally are not.

a. Nonprescription (over-the-counter) oral drug products[15]

Nonprescription drug labels must list "the established name of each inactive ingredient" under the "Inactive ingredients" heading of the Drug Facts label, which appears on the "outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper."[16] This information is visible to consumers at the time of purchase.[17]

[14] See current guidelines for the diagnosis and management of celiac disease, such as those published by the American College of Gastroenterology (Rubio-Tapia, Hill, et al. 2013).

[15] The Introduction defines *oral drug products* for the purposes of this guidance.

[16] See 21 CFR 201.66(c), 201.66(d)(8).

[17] See 21 U.S.C. 321(k), 352(c).

b. Prescription oral drug products

Although not currently mandated by FDA's regulations, manufacturers of prescription oral drug products generally provide a list of inactive ingredients in the DESCRIPTION section of the prescribing information.[18]

Drugs that are licensed biological products (i.e., they are regulated under a biologics license application (BLA)) are subject to additional labeling requirements described in 21 CFR part 610, subpart G. In particular, 21 CFR 610.61 requires identification of certain types of inactive ingredients, including preservatives, "known sensitizing substances," and "inactive ingredients when a safety factor."

We interpret the requirement that inactive ingredients be identified in the labeling of biological products "when a safety factor" as meaning that *wheat gluten* and *wheat flour* must be identified by those names if they are present in orally administered biological products.

2. Established Names

According to section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the term *established name* means (a) the official name designated pursuant to section 508;[19] (b) if there is no such name, the title of a monograph for the ingredient in an official compendium;[20] or (c) the "common or usual name" if neither (a) nor (b) applies.

Consistent with this provision, the established name used in labeling for any wheat-derived ingredient that is the subject of a monograph in an official compendium must be the monograph title, where there is no official name designated pursuant to section 508. For example, *wheat starch* (not *starch*) is the established name by which wheat starch must be identified in drug labeling. However, the more highly processed ingredients discussed in section II.A of this guidance (ingredients derived from starch and ingredients produced by fermentation) do not include a botanical source such as wheat in the established name of the ingredient because the titles of their compendial monographs do not include this designation.

If an ingredient is not recognized in an official compendium and does not have an applicable official name designated pursuant to section 508 of the FD&C Act, then it must be identified in

[18] See 21 CFR 201.57 and 201.80. Licensed biological products that meet the statutory definition of drugs under section 201(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) are subject to the labeling requirements of part 201 (except as otherwise indicated, e.g., section 201.1(m)) and drug labeling provisions of the FD&C Act, and thus also bear labeling in Physician Labeling Rule (PLR) format or non-PLR format.

[19] We do not routinely designate official names for excipients; see 21 CFR 299.4(e).

[20] An official compendium is one cited in the FD&C Act. This includes the USP, NF, and the Homeopathic Pharmacopoeia of the United States. See section 201(g) of the FD&C Act.

labeling by its common or usual name.[21] Wheat gluten and wheat flour fall into this category, and we consider *wheat gluten* and *wheat flour* to be their appropriate common or usual names.[22]

3. Section 502(f) of the FD&C Act

Section 502(f) of the FD&C Act states that a drug "shall be deemed to be misbranded . . . unless its labeling bears . . . such adequate warnings against use in those pathological conditions . . . where its use may be dangerous to health . . . in such manner and form, as are necessary for the protection of users."

We are not aware of any currently marketed oral drug product that contains wheat gluten as an intentionally added inactive ingredient. If such a product exists, we would expect *wheat gluten* to be included in its labeled list of inactive ingredients. If the labeling fails to disclose wheat gluten as an inactive ingredient, we would consider whether the product is misbranded under section 502(f) or other authorities (e.g., 21 CFR 201.66(c)(8)) in the case of a nonprescription oral drug product).

III. RECOMMENDATIONS

We encourage drug manufacturers to have accurate information about their products' gluten content available so they can respond to questions from consumers and health care professionals. Manufacturers should pay attention to possible sources of gluten in their products, consider specifications when appropriate, and consider the impact of changes in ingredient sources or formulations on gluten content.

A. Voluntary Statements Regarding Gluten

1. Statements on Labels or in Required Labeling

We recommend that drug manufacturers that wish to make statements about gluten anywhere on oral drug product labels or in required labeling use the following statement, when it is truthful and substantiated:

Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).[23]

We would interpret such a statement to mean that the manufacturer knows that no ingredient in the product was derived directly or indirectly from wheat, barley, or rye or their crossbred hybrids. This would preclude, for example, the use of ingredients derived from wheat starch or from starch of unknown botanical origin. It would also preclude the use of ingredients produced

[21] See section 502(e)(3) of the FD&C Act.

[22] *Wheat gluten* is the name given to the ingredient in FDA's GRAS (generally recognized as safe) affirmation regulation for wheat gluten (21 CFR 184.1322). See also 21 CFR 137.105, which specifically mentions wheat flour.

[23] For the remainder of this guidance, we use the phrase *recommended labeling statement* to mean this statement or minor variations with equivalent meaning and specificity.

through a fermentation process if the fermentation medium is not known to be free of ingredients derived from wheat, barley, or rye or their crossbred hybrids. Substantiation for such a statement is discussed in section III.A.2 of this guidance.

We encourage use of this recommended labeling statement to provide health care professionals and consumers with consistent, clear, accurate, and readily understood information about the gluten content of the pharmaceutical products they use. Furthermore, this phrase allows easy searching for terms such as *gluten* and *wheat*. This recommended labeling statement does not describe a drug as *gluten-free* because we have not established criteria for gluten-free statements on oral drug products, and it may be difficult to substantiate that a drug product is free of gluten. We are not aware of analytical test methods currently validated to detect or quantify gluten in finished drug products or in drug ingredients at the low levels at which it would generally be expected to be present, if at all. Furthermore, we have not determined whether a gluten-free statement on an oral drug product should refer to an absence of intact gluten or whether such a statement should also require an absence of gluten peptides.

2. Supporting Information

Firms are responsible for the truthfulness of their gluten-related labeling statements and for ensuring that the information related to their oral drug products supports the use of such statements.[24] Firms should also have supporting information available, including information from ingredient suppliers about their processes and raw materials. Indeed, CGMP regulations include recordkeeping requirements encompassing information that may be relevant.[25]

For firms wishing to use the recommended labeling statement, substantiation for such a statement should include a written commitment from ingredient suppliers that, for each ingredient potentially derived from wheat, barley, rye, or their crossbred hybrids or produced through fermentation, these grains are not used in the production of the ingredient.

For statements other than the recommended labeling statement, the supporting information could vary by product. For example, firms may be able to test individual wheat-derived ingredients for the absence of nitrogen (indicating an absence of all protein, including gluten), or they may be able to provide information demonstrating that the processing of such ingredients removes the gluten. If such ingredient testing is conducted, the manufacturing records[26] must include the results of any tests and the conclusions derived from them.[27] These records must be readily available to FDA for authorized inspection.[28]

[24] See section 502(a) of the FD&C Act (21 U.S.C. 352(a)).

[25] See, e.g., 21 CFR 210.3(b)(3), 211.180(c), 211.184(c), 211.186(b)(9), 211.194(a).

[26] In this guidance, we use *manufacturing records* as an umbrella term to refer to the records discussed in 21 CFR 211.184–211.194.

[27] See 21 CFR 211.184(b).

[28] See 21 CFR 211.180(c).

B. Submission and Adoption

1. Oral Drug Products With New or Pending Applications

An applicant submitting a new drug application (NDA), abbreviated new drug application (ANDA), or BLA that wishes to use the recommended labeling statement must ensure that its use is consistent with the information in the application related to the oral drug product ingredients.[29] We are not asking that applicants submit additional specific information to their applications, such as the supplier agreements referred to above, but applicants should ensure that such information is available. An applicant that wishes to use an alternative statement should propose in the application how it intends to support the alternative statement.

2. Oral Drug Products With Approved Applications

An NDA, ANDA, or BLA holder with an approved application who seeks to change a product formulation to make a gluten statement should refer to relevant regulations and guidance regarding submission requirements associated with the formulation changes.[30]

An NDA, ANDA, or BLA holder seeking to include the recommended labeling statement who can properly substantiate it without changes to the approved product formulation may revise labeling at any time to do so. The addition of the recommended labeling statement may then be reported in the next annual report, pursuant to 21 CFR 314.70(a)(3) and 601.12(a)(3).[31]

An NDA, ANDA, or BLA holder wishing to use an alternative statement must submit the proposed statement and information that supports its use in a prior approval supplement (PAS). The addition of an alternative statement that communicates something different from or in addition to the absence of ingredients made from gluten-containing grains (wheat, barley, or rye) requires the submission and review of data not already included in the application.[32]

Regarding labeling requirements specific to generic drugs, a firm marketing a product described in an ANDA can include either the recommended labeling statement or an alternative statement addressing gluten—even if the reference listed drug (RLD) for the product described in the ANDA does not include such a statement—as long as the submission provisions described above

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[29] See section 502(a) of the FD&C Act (21 U.S.C. 352(a)).

[30] See 21 CFR 314.70(b)(2)(i), 601.12(b)(2)(i) and relevant FDA guidance documents including *Changes to an Approved NDA or ANDA* and the *Scale-Up and Post-Approval Changes (SUPAC)* documents. We update guidances periodically. For the most recent version of a guidance, check the FDA Drugs guidance Web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[31] Under 21 CFR 314.70(b)(2)(v)(A) and 601.12(f)(1), a labeling change that does not fall into enumerated categories is to be submitted as a prior approval supplement (PAS). However, under 21 CFR 314.70(a)(3) and 601.12(a)(3), an applicant is required to make a change in accordance with a regulation or guidance that provides for a less burdensome notification of the change than a PAS. Pursuant to these regulations, we are providing that notification may be made in an annual report when labels or labeling are changed to include the recommended labeling statement, without other changes to the product.

[32] See 21 CFR 314.70(b)(2)(v)(A), 601.12(f)(1).

are satisfied and the recommended labeling statement is properly substantiated or the alternative statement is approved. Conversely, if the RLD for a product described in an ANDA includes either the recommended labeling statement or an alternative statement addressing gluten, the product described in the ANDA is not required to include such a statement in its labeling to comply with the same labeling requirement that applies to ANDAs. Although the labeling of a product described in an ANDA and its RLD must generally be the same, an exception is made for differences attributable to the products being produced or distributed by different manufacturers. Such differences may include differences in labeling to reflect permissible differences in the formulation of the drug products (such as permissible differences in inactive ingredients) and labeling revisions made to comply with current FDA labeling guidelines or other guidance. See section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314.94(a)(8)(iv).

3. Oral Drug Products With Approved Applications That Already Include a Statement About Gluten Other Than the Recommended Labeling Statement

We are aware that some marketed oral drug products already include a gluten labeling statement other than the recommended labeling statement described in this guidance. Firms are encouraged to determine whether they will revise their labeling to use the recommended labeling statement or whether they have an adequate basis for the continued use of an alternative statement.

If a firm chooses to adopt the recommended labeling statement and this action does not require changes in the product formulation (or is not combined with another change that requires submission of a supplement), the firm may submit this labeling change in an annual report to the NDA, ANDA, or BLA (21 CFR 314.70(a)(3), 601.12(a)(3)).

However, if adopting a gluten labeling statement requires changes in the product formulation (or is combined with other labeling changes that require a PAS), the application holder must submit the change in a PAS.[33]

4. Nonapplication Oral Drug Products

For oral drug products marketed without an application, firms may revise their labeling to adopt the recommended labeling statement if the statement is truthful and substantiated.

As noted above, if an oral drug product's labeling already includes a gluten statement, firms are encouraged to review this guidance and determine whether they will revise their labeling to use the recommended labeling statement. If a firm wishes to continue to use a labeling statement other than the recommended labeling statement, the firm is responsible for the truthfulness of such a statement and for ensuring that the information related to the oral drug product supports its use.[34]

[33] See 21 CFR 314.70(b)(2)(i), 601.12(b)(2)(i).

[34] See section 502(a) of the FD&C Act (21 U.S.C. 352(a)).

C. Placement of a Voluntary Gluten Labeling Statement

1. Prescription Oral Drug Products

When used, a voluntary gluten statement should be included in the DESCRIPTION section of the prescribing information. Specifically, it should appear at the end of the inactive ingredients list. If the oral drug product has associated FDA-approved patient labeling, the statement should also appear in that patient labeling, either at the end of an inactive ingredients list or at the end of the patient labeling, after the name and address of the manufacturer, packer, or distributor. In addition, if a voluntary gluten statement is included on the immediate container label and, if applicable, carton labeling, it should appear on the side or back panel. The statement should not appear on the principal display panel, to avoid interference with the required or recommended information that appears on labels and labeling.[35]

2. Nonprescription Oral Drug Products

Voluntary gluten statements should be visible at the time of purchase and should appear on the immediate container label and carton labeling in a location outside of the Drug Facts label. The statement must not interfere with the required information that appears on labels and labeling.[36]

IV. REFERENCES

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Kasarda, DD, FM Dupont, et al., 2008, Surface-Associated Proteins of Wheat Starch Granules: Suitability of Wheat Starch for Celiac Patients, J Agric Food Chem, 56:10292–10302.

[35] The prominence, placement, font, and color should be consistent with the concepts described in the draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. When final, this guidance will represent the FDA's current thinking on this topic. See also section 502(c) of the FD&C Act (21 U.S.C. 352(c)) and 21 CFR 201.15, on prominence of required labeling information.

[36] The general labeling requirements in 21 CFR part 201 specify which information must be included on a drug product's labeling and how the information should be presented, among other things. See also section 502(c) of the FD&C Act (21 U.S.C. 352(c)) and 21 CFR 201.15, on prominence of required labeling information.

La Vieille, S, S Dubois, et al., 2014, Estimated Levels of Gluten Incidentally Present in a Canadian Gluten-Free Diet, Nutrients, 6:881–896.

Rubio-Tapia, A, ID Hill, et al., 2013, ACG Clinical Guidelines: Diagnosis and Management of Celiac Disease, Am J Gastroenterol, 108:656–676.

DEC 12 2017

Ms. Meghan O'Hara
[redacted]

Re: Docket No. FDA-2015-P-5081

Dear Ms. O'Hara:

This letter responds to the citizen petition you submitted to the Food and Drug Administration (FDA or the Agency), which we received on December 24, 2015 (Petition). Your Petition asks FDA to require that the presence of gluten in drug products be disclosed when it exceeds 20 parts per million (ppm). More specifically, you ask FDA to issue:

> A regulation in the form of a mandatory rule: that medications disclose when gluten is present in excess of 20 ppm gluten and/or when medications do not meet the conditions of the finalized (currently proposed) FDA rule "Gluten-Free Labeling of Fermented or Hydrolyzed Foods."

(Petition at 1).

Your Petition defines gluten for this purpose as "any gluten grain or any gluten-grain product derivative, whether or not processed to remove gluten" (Petition at 1). We use the term *gluten* in this response letter to mean the proteins that naturally occur in a gluten-containing grain (wheat, barley, rye, or their crossbred hybrids) that may cause adverse health effects in persons with celiac disease (e.g., prolamins and glutelins).[1]

We have carefully considered your Petition and comments submitted to the docket. We appreciate the effort you have undertaken to improve the welfare of individuals with celiac disease. For the reasons explained below, we are denying the specific request made in your

[1] This use matches the definition in our food labeling regulations (21 CFR 101.91(a)(2)), which require that manufacturers wishing to voluntarily label foods as "gluten-free" must ensure that the foods meet certain criteria. If we were to grant your Petition, we would find your proposed definition of *gluten* difficult to work with because, when combined with your requested action, your definition would seem to require gluten labeling statements on drug products triggered, for example, by the presence of a wheat-derived ingredient (including one that was highly processed to remove gluten, such as distilled ethanol) if the *ingredient* is present in the finished drug product above 20 ppm, even if gluten is not present in the ingredient. We have, however, also considered your requested action as encompassing a labeling requirement triggered by the presence of *gluten* (as defined in § 101.91(a)(2)) above 20 ppm in a finished drug product.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Petition, but we are addressing in a different way the concern some individuals with celiac disease have about the possible presence of gluten in drug products. Today, FDA is announcing the availability of a draft guidance for industry, *Gluten in Drug Products and Associated Labeling Recommendations* (draft guidance), a copy of which is enclosed with this response letter.[2] We are issuing this draft guidance for public comment, consistent with our regulations concerning good guidance practices (21 CFR 10.115). The information in the draft guidance is intended to convey to drug manufacturers FDA's recommendations on how certain drug products should be labeled regarding gluten, a matter of interest to individuals with celiac disease. Importantly, the draft guidance encourages drug manufacturers wishing to make statements to voluntarily label their products with the statement "Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye)," when that statement is truthful and properly substantiated.

Broadly, your petition asks FDA to require disclosure of gluten if it is above 20 ppm in a drug product. With respect to hydrolyzed or fermented ingredients, your petition essentially asks FDA to apply to drugs the same requirements for determining compliance the agency may eventually apply to hydrolyzed or fermented ingredients in foods in determining whether these ingredients (or a finished food product to which they are added) contain gluten above 20 ppm. Because the foods rule to which you request conformity is currently a proposed rule, we are not in a position at this time to assess whether the additional requirements for determining compliance with the foods rule should be applied to drugs. Further, because FDA does not plan to require affirmative "contains gluten" disclosures on drug labels at this time, it is not necessary to detail our recommendations concerning the labeling of drug products containing hydrolyzed or fermented ingredients.

I. Background

A. Nature of Celiac Disease

Celiac disease is an immune-mediated chronic inflammatory disorder affecting primarily the small intestine in genetically susceptible individuals. In these individuals, the consumption of gluten stimulates the production of antibodies and inflammatory cells, resulting in an abnormal immune response. The resultant immediate inflammatory reaction damages the tiny, fingerlike protrusions called villi that line the small intestine and absorb nutrients from food. Over time, continued dietary exposure to gluten can lead to impaired absorption of nutrients and other serious health problems.

The standard treatment for individuals with celiac disease is the elimination of gluten-containing products from their diets. Avoidance of gluten can resolve the symptoms, mitigate and possibly reverse intestinal damage, and reduce the health risks associated with celiac disease.[3]

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[2] The draft guidance is available on FDA's Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[3] See Rubio-Tapia, Hill, et al., [American College of Gastroenterology] ACG Clinical Guidelines: "Diagnosis and Management of Celiac Disease *Am J Gastroenterology"* (2013); 108:656-676 (hereinafter "2013 ACG Clinical

B. Previous Petition Concerning Gluten in Drug Products

As you know, on May 12, 2015, FDA responded to a previous petition concerning gluten in drug products (previous petition), granting it in part and denying it in part.[4] The previous petition asked FDA to exclude the use of wheat gluten as an inactive ingredient in prescription and over-the-counter (OTC) drug products unless an exception was necessary. The previous petition also asked FDA to require drug labeling to identify wheat gluten when it is added to a drug as an inactive ingredient.

Before responding to the previous petition, FDA solicited information and comments from the public concerning drug ingredients potentially derived from wheat, barley, or rye (see FDA's December 21, 2011, published request for information (76 FR 79196), Docket No. FDA-2011-N-0842).

FDA's response to the previous petition explained that wheat gluten itself has rarely been added to drug products marketed in the United States. We are not aware of any currently marketed oral drug product that contains wheat gluten as an intentionally added inactive ingredient. If wheat gluten were added to a drug product — as an active or inactive ingredient — it should be identified as such in product labeling.

We understood the previous petitioner as also being concerned with trace levels of gluten potentially present unintentionally in drug products. For this reason, our response to the previous petition identified the various ways in which gluten may be introduced unintentionally into an oral drug product (e.g., as an impurity present at low levels in wheat starch). We determined that drug ingredients are rarely derived from wheat, barley, or rye, and that a wheat-derived ingredient may contribute only a small amount of gluten, less than 0.5 milligrams (mg), to a unit dose of an oral drug product. Thus, the amount of gluten estimated to be potentially present in a unit dose of an oral drug product (less than 0.5 mg) is significantly less than the range at which gluten is estimated to be present in a gluten-free diet (5 to 50 mg) (La Vieille, Dubois, et al. 2014; Catassi, Fabiani, et al. 2007).[5] In addition, even a single serving of food properly labeled "gluten-free" could contain more gluten than this (i.e., 20 ppm or up to 0.6 mg gluten in a 30-gram serving of food labeled gluten-free). In view of this information, FDA determined that new labeling requirements concerning low levels of gluten potentially present in drug products would not be the appropriate means to address the concerns raised.

Both your Petition and the previous petition have conveyed, however, that some individuals with celiac disease and their care-givers have difficulty obtaining assurance that needed medications

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Guidelines" or "the Guidelines"). These guidelines are referenced in your Petition and were also referenced in our previous petition response, Docket No. FDA-2008-P-0333.

[4] See FDA's citizen petition response (Docket No. FDA-2008-P-0333), available at http://www.regulations.gov.

[5] We recognize that gluten-free diets may be highly variable, and that individuals diagnosed with refractory celiac disease may have more restrictive diets.

will not harm them. For that reason, FDA has developed the approach to gluten in drug products described below.

C. FDA's Current Approach to Gluten in Drug Products

FDA's current approach to the possible presence of gluten in drug products involves the following four elements. FDA is engaged in efforts to:

- Encourage manufacturers that wish to make statements about gluten on oral drug product labels or in required labeling to voluntarily label their products with the statement, "Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye)," when that statement is truthful and properly substantiated.

- Educate consumers that unless a drug product is labeled as containing wheat gluten or wheat flour as an ingredient, the product is not expected to contain more gluten than can be present in a single serving of food labeled gluten-free.

- Encourage manufacturers to pay attention to possible sources of gluten in drug products (e.g., wheat starch), consider specifications when appropriate, and consider the impact of changes in ingredient sources or formulations on gluten content.

- Encourage manufacturers to have accurate information about their products' gluten content available so they can respond to questions from consumers and health care professionals. For example, an individual with refractory or nonresponsive celiac disease may want to know whether a drug product contains any ingredient derived from wheat, barley, or rye, in the absence of the voluntary labeling claim discussed in FDA's draft guidance.

1. Amounts of Gluten Potentially Present in Oral Drug Products Versus Gluten-Free Foods

FDA developed its current approach after determining that most oral drug products do not contain ingredients derived from wheat, barley, or rye. The likelihood of them including more than one such ingredient is even less. Thus, it is expected that the amount of gluten potentially present in a unit dose of an oral drug product is less than the amount of gluten that could potentially be found in a single serving of a cookie (30 grams) labeled *gluten-free* in accordance with FDA's regulations at 21 CFR 101.91 (if all of the criteria of that regulation are satisfied).[6]

We also considered how much gluten may be present in a gluten-free diet (not just an individual serving of food). In a study intended to establish a safe level of gluten ingestion in individuals with celiac disease, Catassi et al. concluded that the test subjects' background exposure to gluten

[6] A 30-gram serving of food, corresponding to a single cookie, for example, could contain up to 0.6 mg gluten while bearing a gluten-free statement if the criteria for the definition of *gluten-free* are satisfied. 30 grams x 20 ppm=0.6 mg. See reference amounts customarily consumed per eating occasion in FDA's food labeling regulations, 21 CFR 101.12, Table 2.

in a gluten-free diet was < 5 mg per day during the course of the study and that more generally "the daily ingestion of contaminating gluten in apparently well-treated CD patients is most likely to range from 5 to 50 mg."[7] We also reviewed a Canadian study estimating that gluten-free diets contain low-milligram quantities of gluten, approaching 50 mg per day in certain circumstances.[8]

In summary, we conclude that — apart from the very rare drug product to which wheat gluten or wheat flour itself may be intentionally added, and should be indicated in product labeling — the amount of gluten in a unit dose of any oral drug product (i.e., the amount of gluten that may be present either adventitiously or as a constituent of inactive ingredients derived from wheat) is likely to be:

- Less than the amount of gluten that may be present in a single serving of food labeled gluten-free, provided that food met all the criteria for gluten-free labeling

- Several times less than the range at which gluten is estimated to be present in a gluten-free diet (5 to 50 mg per day) (La Vieille, Dubois, et al. 2014; Catassi, Fabiani, et al. 2007)

This leads us to conclude that individuals with celiac disease who do well on a gluten-free diet need not be concerned about the possible presence of gluten in drug products — apart from the very rare drug product to which wheat gluten or wheat flour itself may be intentionally added and should be indicated in labeling. We are aware of no such drug products marketed in the United States today.

2. Safe Levels of Exposure

As stated in our previous petition response, opinions vary regarding low levels at which gluten may be safely ingested by individuals with celiac disease. It has been estimated that daily gluten ingestion of less than 10 mg is unlikely to cause significant histological abnormalities (i.e., microscopic tissue changes in the small intestines).[9] FDA recognizes that there is not a single, well-established safe level of exposure and that some individuals with celiac disease are expected to be more sensitive than others. FDA's Center for Food Safety and Applied Nutrition (CFSAN) prepared a report titled "Health Hazard Assessment for Gluten Exposure in Individuals with Celiac Disease: Determination of Tolerable Daily Intake Levels and Levels of Concern for

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[7] Catassi, et al., "A prospective, Double-Blind, Placebo-Controlled Trial to Establish a Safe Gluten Threshold for Patients With Celiac Disease," Am J Clin Nutr (2007); 85: 160-166.

[8] La Vielle, Dubois, et al. "Estimated Levels of Gluten Incidentally Present in a Canadian Gluten-Free Diet," *Nutrients* (2014); 6, 881-896.

[9] See Akobeng and Thomas, "Systematic Review: Tolerable Amount of Gluten for People With Coeliac Disease," *Aliment Pharmacol Ther,* 27 (2008); 1044-1052, (cited in the 2013 ACG Clinical Guidelines).

Gluten," (Health Hazard Assessment for Gluten Exposure), dated May 2011, in connection with its rulemaking to establish criteria for voluntary gluten-free claims on food.[10]

When soliciting public comments on the Health Hazard Assessment for Gluten Exposure, CFSAN announced its tentative conclusion that the safety assessment-based approach reflected in this document was a "conservative, highly uncertain estimation of risk to individuals with celiac disease associated with very low levels of gluten exposure."[11] CFSAN ultimately did not rely on this health hazard assessment in adopting its final rule defining criteria for voluntary gluten-free claims for food, instead referring to its approach as being "analytical methods-based" (i.e., reflecting the fact that 20 ppm is currently the lowest level at which analytical methods have been scientifically validated to reliably and consistently detect gluten across a range of food matrices). When adopting its final rule, CFSAN again noted that its health hazard assessment may be conservative and highly uncertain and also explained that the definition in the final rule was expected to be protective of the large majority of individuals with celiac disease.[12]

3. Nonresponsive or Refractory Celiac Disease

We have reviewed clinical guidelines for the diagnosis and management of celiac disease prepared by the American College of Gastroenterology (ACG),[13] paying attention to its recommendations for individuals who do not appear to respond well to a gluten-free diet. The 2013 ACG Clinical Guidelines state that nonresponsive celiac disease may affect 7 to 30 percent of celiac disease patients treated with a gluten-free diet. The guidelines recommend confirmation of the initial celiac disease diagnosis as a first step in evaluating such patients. The guidelines state that when the diagnosis is confirmed, non-adherence to a gluten-free diet, either purposeful or inadvertent, is the most common cause of nonresponsive celiac disease, identified in 35 to 50 percent of cases. The 2013 ACG Clinical Guidelines define refractory celiac disease as persistent or recurrent symptoms and signs of malabsorption with small-intestinal villous atrophy despite a strict gluten-free diet for more than 12 months and in the absence of other disorders. The guidelines state that refractory celiac disease is uncommon, affecting 1 to 2 percent of individuals with celiac disease.

We conclude from this information that:

- An individual with celiac disease who does not respond well after being advised to follow a gluten-free diet may, with the help of a health care provider, consider whether intentional or inadvertent ingestion of gluten is the cause. Such an evaluation would

[10] The Health Hazard Assessment for Gluten Exposure is available at http://www.fda.gov/downloads/Food/FoodScienceResearch/UCM264152.pdf.

[11] "Food Labeling; Gluten-Free Labeling of Foods; Reopening of the Comment Period," 76 FR 46671, August 3, 2011.

[12] "Food Labeling; Gluten-Free Labeling of Foods; Final Rule," 78 FR 47154 at 47160, August 5, 2013.

[13] 2013 ACG Clinical Guidelines (see footnote 3).

sensibly focus on dietary gluten as a larger possible source of gluten exposure than oral medications.

- If further reduction of dietary gluten does not help an individual with nonresponsive celiac disease, the possibility of gluten exposure from oral drug products might be explored.

- *Refractory* celiac disease is rarer than *nonresponsive* celiac disease, as those terms are used in the 2013 ACG Clinical Guidelines. Individuals diagnosed with refractory celiac disease require very specialized care. These individuals may make up roughly 0.02 percent of the U.S. population (1 to 2 percent of individuals with celiac disease, who comprise approximately 1 percent of the U.S. population).

FDA's current approach to gluten in drug products fits this understanding. Individuals diagnosed with celiac disease who do not respond well to a gluten-free diet will be able to seek out drugs that bear the voluntary claim that the product "contains no ingredient made from a gluten-containing grain (wheat, barley, or rye)." Individuals who are diagnosed with refractory celiac disease, for example, might inquire into the gluten status of any needed drugs not bearing such a labeling claim, and review, with their health care providers, the risks and benefits of any oral medications that are believed to present a risk of low-level gluten exposure.

4. Requested Affirmative Gluten Disclosure Requirement

Based on the foregoing information and analysis, we do not currently plan to propose new regulations in this area, such as a requirement to include "contains gluten" labeling on a drug product if gluten is present above a defined threshold, such as 20 ppm. If we were to adopt the threshold requested in your Petition (20 ppm or 0.02 mg gluten per gram of drug), such labeling could effectively warn all individuals with celiac disease away from taking certain drug products not expected to harm the vast majority of them. As indicated in our previous petition response, if we become aware of new information suggesting that drugs contain gluten in amounts harmful to most individuals with celiac disease or in amounts that would significantly increase cumulative exposure to gluten in a gluten-free diet, we will re-evaluate available options.

II. FDA's Analysis of Information and Arguments Included in the Petition

The information and arguments presented in your Petition do not persuade us that the approach we have developed should be changed. We address the information and arguments presented in your Petition below.

A. Crowe and Falini Note

Your Petition refers to a note published in 2001 in the *American Journal of Health-System Pharmacy* concerning gluten in drug products (Petition at 3-4).[14] You state that the reported

[14] Crowe and Falini, "Gluten in Pharmaceutical Products," *Am J Health-Syst Pharm* (2001); 58:396-401.

information was not considered in FDA's previous petition response and state that it supports the action requested in your Petition. Although the Crowe and Falini note was not referenced in our previous petition response, FDA was aware of it and reviewed it before responding to the previous petition.

The note describes a survey in which drug manufacturers were asked several questions about the gluten content of their drugs. The survey asked manufacturers whether they had a policy of producing gluten-free products; if so, whether they guaranteed the gluten-free status of their products; and whether they could identify products known to be gluten-free, among other questions. The note does not include a discussion of what is meant by the term "gluten-free." It is not surprising to FDA that most survey participants would have declined to respond that their drug products are gluten-free if that term may be assumed to mean zero gluten content, given the possibility of adventitious contamination at trace levels.

FDA's current approach to the possible presence of gluten in oral drug products is informed by a detailed analysis of possible sources of gluten in oral drug products and the maximum amounts at which gluten is reasonably expected to be present, as described above. Importantly, our current approach should support reliable labeling statements for oral drug products informing interested consumers and health care providers that a product bearing the statement "contains no ingredient made from a gluten-containing grain (wheat, barley, or rye)" when such a statement is truthful and properly substantiated.

B. Adventitious Contamination

Your Petition mentions the possibility of "cross contamination" of drug products with gluten, which we understand to mean the unintended transfer of gluten from a surface or object into a drug product. For example, your Petition states on page 4 that "while some companies say 'all of our medications are gluten free,' it is more common to hear a version that 'none of the ingredients in the medication contain gluten, but we do not test for it and cannot guarantee against cross contamination.'"

In our draft guidance, we refer to this type of contamination more broadly as "adventitious contamination," encompassing any unintended introduction of gluten into a drug product or drug ingredient as a result of contact with gluten or contamination with a gluten-containing grain during manufacture, processing, transportation, or storage, and not as a result of gluten being inherently present in an ingredient.

We have considered whether the amount of gluten that could — in theory — be introduced into a drug product adventitiously would be expected to harm an individual with celiac disease. More specifically, we have considered how much gluten might be introduced into an oral drug product (1) as a result of wheat being present adventitiously in, for example, corn used to make corn starch or other corn-derived ingredients; or (2) because the drug product or an ingredient used in the drug product came into contact with gluten inadvertently during manufacture, processing, or storage. In either case, we do not believe such adventitious contamination will result in more

than a few micrograms[15] of gluten in a unit dose of an oral drug product (i.e. less than 15 micrograms). This amount is a small fraction of the amount of gluten that may be present daily in a gluten-free diet (5 to 50 mg). Accordingly, we do not believe questions to manufacturers about whether a drug product was manufactured in a "gluten-free facility" will generate particularly meaningful information for most individuals with celiac disease.

Our analysis regarding adventitious contamination applies to products manufactured in accordance with current good manufacturing practices (CGMPs) for drugs.[16]

C. Excipients as Possible "Hidden Sources" of Gluten in Drug Products

Your Petition states on page 5 that researchers continue to mention drug excipients as possible hidden sources of gluten in drug products. As an example of this, you cite an article published in 2015 in the *BMJ* (originally called the *British Medical Journal*).[17] This article asserts that "drug fillers" are hidden sources of gluten but does not identify specific ingredients or amounts of gluten at issue. Nothing in this article adds to or calls into question our detailed analysis of possible sources of gluten in oral drug products, focusing on the maximum amounts at which gluten is reasonably expected to be present.

D. Sources of Information About the Possible Gluten Content of Drug Products

Your Petition references a Web site, www.glutenfreedrugs.com, as covering only a small fraction of drugs marketed in the United States and not being up to date (Petition at 4). We do not intend for consumers to rely on third-party Web sites or publications in place of labels or required labeling to obtain current information about the composition of drug products.

As discussed above, information currently available to us indicates that marketed drug products do not contain "hidden gluten" in amounts that would harm a typical individual with celiac disease. Furthermore, voluntary labeling statements about the absence of ingredients derived from wheat, barley, or rye, as described in our draft guidance, should provide information reassuring to individuals with celiac disease.

E. Assertion That the Gluten Content of Wheat Starch Can Vary Widely

[15] A "microgram" is one one-millionth of a gram or roughly one one-millionth the weight of a paperclip. A "milligram," by contrast, is one one-thousandth of a gram.

[16] See generally 21 CFR part 210 (Current Good Manufacturing Practice in Manufacturing, Processing, Packing, or Holding of Drugs; General) and 21 CFR part 211 (Current Good Manufacturing Practice for Finished Pharmaceuticals).

[17] Lebwohl, Ludbigsson et al., "Cealiac Disease and Non-Celiac Gluten Sensitivity," *BMJ* (2015); 351:h4347.

Your Petition states on page 5 that amounts of gluten present in wheat starch can vary widely, from less than 5 ppm to over 10,000 ppm, citing published Proceedings of the 27th Meeting Working Group on Prolamin Analysis and Toxicity (WGPAT).[18]

We have reviewed the published WGPAT Proceedings referenced in the Petition. Section 4.2 reports on a study carried out at the German Research Center for Food Chemistry, and it includes the information referenced in the Petition, that wheat starch samples have been found to contain gluten in amounts that vary widely, from less than 5 ppm to more than 10,000 ppm.

The reported information does not change our current estimates regarding the amount of gluten potentially present in drug products that contain ingredients derived from wheat, barley, or rye. The referenced study reports analytical results for 22 wheat starch samples using three different test methods. The wheat starch samples tested are not identified in the report, except by sample number, so it is not clear whether they are intended for use in foods, drugs, or other applications. Nineteen of the 22 samples contained less than 300 ppm gluten according to all three test methods. Three of the samples were found to contain significantly higher amounts of gluten, ranging up to 10,189 ± 293 ppm. Because the researchers were evaluating the performance of the test methods, it is understandable that they might select wheat starch samples having a range of gluten content, to evaluate the performance of the test methods over this range.

1. Wheat Starch Containing More Than 3,000 ppm Gluten

We do not expect that wheat with the high-gluten content observed in certain samples would be used in drug products. The NF monograph for wheat starch specifies that wheat starch NF contains not more than 0.3 percent (3,000 ppm) total protein. Gluten makes up some fraction (but not all) of the total protein content of wheat starch. Any wheat starch containing more than 3,000 ppm (or even approaching 3,000 ppm) gluten would not satisfy the NF monograph's total protein limit. This allows us to conclude that the wheat starch samples found to contain the highest gluten content, reported in the WGPAT proceedings (in the range of 6,000 and 10,000 ppm), would not be selected for use in drug products marketed in the United States.[19]

2. Actual Gluten Content of Wheat Starch NF

Our estimate regarding the maximum amount of gluten reasonably expected to be introduced into an oral drug product because gluten is present in an inactive ingredient (not more than 0.5 mg per unit dose) is based in part on our expectation that wheat starch NF contains no more than

[18] Konitzer, Wieser, et al. "Quantitation of Gluten in Wheat Starch by Gel Permeation Chromatography With Fluorescence Detection," (2014); Proceedings of the 27th Meeting Working Group on Prolamin Analysis and Toxicity (PWG), Koehler, ed., German Research Centre for Food Chemistry, Freising.

[19] The National Formulary is an official compendium, as stated in section 201(j) of the FD&C Act (21 U.S.C. 321(j)). Section 501(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 351(b)) states that any drug is adulterated if it "purports to be or is represented as a drug the name of which is recognized in an official compendium, and its strength differs from, or its quality or purity falls below, the standards set forth in such compendium." See also section 201(g) of the FD&C Act (21 U.S.C. 321(g)), defining "drug."

500 ppm gluten. As stated above, the National Formulary limits total protein in wheat starch to not more than 0.3 percent. According to published reports we have reviewed, wheat starch samples having total protein content within the National Formulary limit (not more than 0.3 percent total protein) do not contain more than 500 ppm gluten. See Skerritt and Hill[20] and Kasarda et al.[21]

Therefore, the information referenced in your Petition does not change our views about the maximum amounts of gluten reasonably expected to be present in any oral drug product that contains inactive ingredients derived from wheat, barley, or rye, and, in fact, reinforces our view that our estimate is conservative (i.e., our estimate likely exaggerates actual maximum amounts of gluten potentially present in oral medication).

F. Drug Product Use Has Increased Since 2001

Your Petition asserts that drug product use has increased since 2001, when the Crowe and Falini note was published, and that the number of drugs on the market has increased, so that an unacceptably small percentage of them are addressed at the glutenfreedrugs Web site. As stated above, we do not expect consumers to rely on third-party Web sites in place of labels or required labeling for information about the composition of drug products. The draft guidance we issued today is intended to facilitate statements in drug labeling that should communicate helpful information to individuals who are concerned about the possible presence of gluten in oral drug products.

G. Generic Substitution

Your Petition makes the point that pharmacies may switch from one generic equivalent of a drug product to another (Petition at 6). We agree with this observation and additionally acknowledge that pharmacists may also substitute a therapeutically equivalent generic product for a brand name product when presented with a prescription for the brand name product. Because the inactive ingredient composition may, at times, vary between a brand name product and its generic equivalents and among the generic equivalents, the possibility that gluten is present at low levels may vary from one product to the next.

Consistent with the analysis presented above, the majority of individuals with celiac disease (those who do well on a gluten-free diet) should not need to worry about the potential presence of gluten at very low levels in oral drug products — whether they are generic or brand name products. Apart from the very rare (and currently non-existent in the United States to our knowledge) drug products that would be labeled as containing wheat gluten or wheat flour as an intentionally added ingredient, oral drug products should not contain more than a very limited amount of gluten, if any.

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[20] Skerritt and Hill, How "Free" is "Gluten Free"? Relationship Between Kjeldahl Nitrogen Values and Gluten Protein Content for Wheat Starches," *Cereal Chem.* (1992); 69(1):110-112.

[21] Kasarda, Dupont, et al., "Surface-Associated Proteins of Wheat Starch Granules: Suitability of Wheat Starch for Celiac Patients," *J. Agric. Food Chem.* (2008); 56, 10292–10302.

Following the issuance of our draft guidance, we expect individuals who wish to avoid even the very low levels of gluten potentially present in oral drug products to have an easier time identifying drugs that contain no ingredients derived from wheat, barley, or rye. We are also hopeful that drug manufacturers not making such claims on their labels will follow our recommendations and have helpful information available for individuals who inquire about the gluten status of their products.

As suggested in your Petition, we agree that individuals interested in the possible gluten content of an oral drug product should distinguish between individual products, including between a brand name product and corresponding generic equivalents and among those generic equivalents. Claims about the absence of ingredients derived from wheat, barley, or rye from a drug product will apply only to the specific drug product for which the claim is made. A physician may often be able to help a patient obtain a specific drug product by indicating "dispense as written" on the prescription.

H. Drug Excipient Sourcing

Your Petition makes the point, on pages 6 and 7, that drug ingredients and finished drug products are sourced from all over the world — suggesting that foreign-sourced ingredients may have higher gluten content than we have considered. The Petition does not present new information to us or cite evidence that drug ingredients sourced from outside the United States contain more gluten than domestically sourced ingredients.

We are aware that drug ingredients potentially derived from wheat, barley, or rye may be sourced from around the world. Our estimates regarding amounts of gluten possibly present in oral drug products have always taken this into account.

Regardless of where the ingredient was produced, we expect that inactive ingredients used in finished drug products marketed in the United States would conform to any applicable monographs in the National Formulary or the United States Pharmacopeia, including, where applicable, established limitations on total protein (as previously discussed).

In developing our response to the previous citizen petition concerning gluten (Docket No. FDA-2008-P-0333), we reviewed published information regarding residual gluten levels in wheat starch and other ingredients not limited to U.S.-supplied ingredients. We applied a conservative estimate that such ingredients are not expected to contain more than 500 ppm gluten based, in part, on our understanding that wheat starch NF complying with the 0.3 percent limit on total protein, is not expected to contain more than 500 ppm gluten.

I. Exposure Levels at Which Gluten Can Harm Certain Individuals with Celiac Disease

Your Petition asserts on page 7 that "new evidence reveals that even small amounts of gluten can harm celiacs." Your Petition cites three sources to support this assertion, but they do not alter FDA's existing understanding in this area.

The first source is a link to an Internet page maintained by the University of Chicago. The link currently produces a "page not found" message, but it formerly provided a publication of the University of Chicago Celiac Disease Center titled "Impact" (summer 2008, Vol. 8, Issue 3). The Petition cites this source as stating:

> About 10% of patients diagnosed with celiac disease do not get better on a gluten-free diet. This can be due to many different reasons. The most common is dietary indiscretion (unintentional or intentional), because gluten is present in so many foods and medications.

(Petition at 7).

Apart from its reference to medications, this statement is generally consistent with FDA's understanding of celiac disease and the 2013 ACG Clinical Guidelines referenced above. This source does not, however, provide any support for the suggestion that medications are a significant source of gluten, and FDA's analysis indicates otherwise.

The second source cited is the 2013 ACG Clinical Guidelines referenced above. On page 7, your Petition cites the Guidelines as stating "In adults, the intestine will often fail to heal despite negative serology and absence of symptoms. This lack of healing may increase the risk of lymphoma, bone disease and ultimately the development of refractory CD."

We reviewed the 2013 ACG Clinical Guidelines in developing our response to the previous petition, and we explain in section I.C.3 of this letter how our approach to gluten in oral drug products fits the Guidelines with respect to nonresponsive and refractory patients. With respect to most individuals with celiac disease, the Guidelines state, "[t]he exact level below which gluten is harmless is not known, but a recent review suggests less than 10 mg per day is unlikely to cause damage in most patients."[22]

The third source cited is an article titled "Trace gluten contamination may play a role in mucosal and clinical recovery in a subgroup of diet-adherent nonresponsive celiac disease patients."[23] This article reports on an experimental Gluten Contamination Elimination Diet (GCED) in individuals with nonresponsive celiac disease. The diet was designed to eliminate gluten potentially present by cross contact in many individuals' gluten-free diets by, for example, eliminating many processed foods. The article reports that most patients who respond to a 3- to 6-month course of the GCED are subsequently able to return to a traditional gluten-free diet without the return of symptoms, suggesting that refractory symptoms were likely due to incomplete adherence to a gluten-free diet. This article is consistent with FDA's current understanding of celiac disease in refractory and nonresponsive patients.

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[22] Citing Akobeng and Thomas, "Systematic Review: Tolerable Amount of Gluten for People With Coeliac Disease," *Aliment Pharmacol Ther 27* (February 2008); 1044-1052.

[23] Hollon, Cureton, et al., Trace gluten contamination may play a role in mucosal and clinical recovery in a subgroup of diet-adherent non-responsive celiac disease patients, *BMC Gastroenterology*, 2013, 13:40.

J. Americans with Disabilities Act

Your Petition refers on page 10 to the Americans with Disabilities Act of 1990 (ADA) and 2008 amendments. The ADA prohibits discrimination and ensures equal opportunity for persons with disabilities in employment, state and local government services, public accommodations, commercial facilities, and transportation.[24] You state that eating is included among "major life activities" under the ADA; you refer to the effect of the ADA on a university's meal service plan; and you state that the action requested in your Petition "would support celiac patients' rights as intended by the Americans with Disabilities Act."[25] We do not believe the ADA imposes a legal requirement for FDA to establish gluten labeling requirements for drugs of the kind you have proposed, nor does your petition appear to argue that such a legal obligation exists.

It is the mission of FDA's Center for Drug Evaluation and Research to protect and promote public health, including by helping to ensure that human drugs are safe and effective for their intended use and that they meet established quality standards. Our current approach to gluten in drug products was developed with this mission in mind. The action requested in your Petition might result in drugs that contain as little as 10 or 20 micrograms of gluten per unit dose bearing statements that caution individuals with celiac disease that the product "contains gluten." Such labeling could over-warn, causing concern and discouraging patients from taking needed medications even though the amount of gluten actually present is unlikely to be problematic for the majority of individuals with celiac disease. A measure that could result in that outcome would not be well-designed for protecting and promoting public health. Your Petition's reference to the ADA does not persuade FDA that the action requested in your Petition should be granted.

K. FDA Issuance of Draft Guidance

In our previous petition response, we stated that we intended to issue draft guidance broadly addressing the potential presence of gluten in drug products, and we stated that this guidance may cover voluntary claims about the absence of gluten from drug products. Your Petition objects to this approach, stating "[u]ncertainty over not only what guidelines will be proposed but also when they will be proposed and how effective they might or might not be adds to the uncertainties and stresses currently experienced by affected celiac individuals, pharmacists, and manufacturers."[26]

FDA has finite resources and must prioritize among regulatory initiatives. Our issuance of draft guidance concerning gluten in drug products comes after our previous response to a citizen

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[24] See generally www.ADA.gov, maintained by the Civil Rights Division of the United States Department of Justice.

[25] Petition at 10.

[26] Petition at 12.

petition in which we explained our determination that oral drug products are not expected to contain more gluten per unit dose than may be present in a single serving of food properly labeled gluten-free, and are not expected to contribute significantly to cumulative daily gluten exposure associated with a gluten-free diet. We are hopeful that the guidance, when finalized, will facilitate more reliable, voluntary labeling statements on oral drug products that effectively communicate to individuals with celiac disease that needed oral medications with the statement will not harm them. Your criticism of this approach does not convince FDA that this is not the right approach to pursue at this time. Nevertheless, as stated above, our issuance of the draft guidance does not preclude a future determination, based on a new analysis or new information, that a labeling requirement similar to that requested in your Petition (i.e., an affirmative disclosure requirement) should be pursued.

L. Absolute Quantities of Gluten Exposure Versus Concentration

Your Petition argues on page 15 that gluten may be present in drug products in higher concentrations than the less-than-20-ppm criterion associated with voluntary gluten-free claims on food products and that the concentration at which gluten is present in a drug product may predict harm to individuals with celiac disease, not just the absolute quantity at which it is present. We reject this argument as speculative and unsupported.

First, our determination that oral drug products are not expected to contain more than 0.5 mg gluten per unit dose is a conservative estimate (i.e., an estimate that likely exaggerates actual maximum amounts of gluten potentially present in oral medication). We have not seen analytical results or product specifications for any oral drug product showing this much gluten is actually present in any oral drug product currently marketed in the United States.

Second, your Petition has not provided any data or even a mechanistic theory supporting its contention that gluten concentration may matter more than, or in addition to, absolute quantities of gluten ingested by an individual with celiac disease. We note that published studies reporting on tolerable amounts of gluten exposure in individuals with celiac disease focus on daily amounts rather than concentrations in any one ingested source. See, for example, the Akobeng and Thomas article[27] cited in the 2013 ACG Clinical Guidelines, to which your Petition refers. In fact, clinical studies in which individuals with celiac disease are exposed to controlled amounts of gluten generally involve concentrated amounts administered at one time. See, for example, the study reported by Catassi et al.[28] in which test subjects were randomly assigned to ingest daily, for 90 days, a capsule containing either 10 mg purified gluten, 50 mg purified gluten, or 50 mg corn starch as a placebo. The researchers concluded that "[t]he ingestion of contaminating gluten should be kept lower than 50 mg/d in the treatment of CD" without reference to gluten concentration in any one dietary source.

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[27] Akobeng and Thomas, "Systematic Review: Tolerable Amount of Gluten for People With Coeliac Disease," *Aliment Pharmacol Ther* 27 (February 2008);1044-1052 (cited in the 2013 ACG Clinical Guidelines).

[28] Catassi, et al., "A Prospective, Double-Blind, Placebo-Controlled Trial to Establish a Safe Gluten Threshold for Patients With Celiac Disease," *Am J Clin Nutr* (2007); 85: 160-166.

M. Arguments Against FDA's 30-Gram Cookie Analysis

FDA's previous citizen petition response made the point that a single 30-gram cookie properly labeled gluten-free may contain up to 20 ppm gluten, or 0.6 mg, according to FDA's food labeling regulations (21 CFR 101.91), if all criteria for the definition of gluten-free are met. By contrast, we do not expect oral drug products to contain more than 0.5 mg gluten per unit dose. Therefore, it would be strange for FDA to require gluten labeling on oral drug products containing smaller amounts of gluten than can be present in a single serving of food labeled gluten-free. Your Petition takes issue with this analysis in several respects but does not persuade FDA that our current approach is inappropriate.

Your Petition points out that the experimental Gluten Contamination Elimination Diet (GCED) for nonresponsive celiac patients referred to in the Hollon study discussed above does not include processed foods. FDA understands that nonresponsive and/or refractory celiac patients may require special care and more strict control of gluten in their diets, as outlined in the 2013 ACG Clinical Guidelines and discussed above. Our draft guidance is intended to help individuals who wish to avoid even the small amounts of gluten potentially present in oral drug products (by encouraging drug manufacturers that wish to make statements about gluten on oral drug product labels or in required labeling to voluntarily label their products with the statement "contains no ingredient made from a gluten-containing grain (wheat, barley, or rye)" when that statement is truthful and properly substantiated, and by encouraging drug manufacturers to have accurate information available about their products' gluten content so they can respond to questions from consumers and health care professionals. Our draft guidance is intended to do so without suggesting that oral drug products containing less than 0.5 mg gluten per unit dose are unsafe for all individuals with celiac disease.

Your Petition also points out that cookies are consumed on a discretionary basis, and prescribed medications generally are not. In our analysis, the cookie represents any processed food labeled gluten-free with a 30-gram serving size. Foods with larger serving sizes that are labeled gluten-free could potentially deliver larger quantities of gluten, and a gluten-free diet could deliver low-milligram quantities of gluten per day (see section I.C.1 of this response letter). As discussed above, we recognize that nonresponsive and/or refractory celiac patients may require special care and will likely aim to ingest no gluten at all, from any source, at least for some period of time. FDA's draft guidance is intended to help such individuals without warning all individuals with celiac disease away from taking oral drug products that potentially contain much less gluten than the amount an individual with celiac disease adhering to a gluten-free diet may ingest from food.

In addition, your Petition states that "[i]n the case of an adverse reaction, celiacs can discontinue eating a gluten-free-labeled cookie without causing harm. The same often cannot be said of a decision to discontinue a medication."[29] In our analysis, cumulative daily gluten exposure from all sources is relevant to the well-being of an individual with celiac disease. If an individual's celiac disease is not well controlled, that individual may need to make dietary changes, as suggested by the 2013 ACG Clinical Guidelines and the GCED study. Any such dietary changes

[29] Petition at 16.

would not be likely to focus on a single food product labeled gluten-free.[30] We expect that dietary changes — focusing on the entire diet — could eliminate approximately 10 mg gluten per day from a gluten-free diet,[31] while oral drug products would be expected to contain a fraction of that amount, if any.

N. Position of the Pharmaceutical Industry

In your Petition, you state that you could find no written statements suggesting that the pharmaceutical industry would oppose the action requested in your Petition. You refer to comments submitted to FDA's Docket No. 2011-N-0842 by the International Pharmaceutical Excipients Council (IPEC) and the Consumer Healthcare Products Association (CPHA) (Petition at 16-17). Both sets of comments reacted to a specific set of questions put forth in FDA's published Request for Information ("Gluten in Drug Products; Request for Information and Comments," 76 FR 79196, December 21, 2011).

IPEC stated in its comments that inactive ingredients are often derived from sources other than wheat, barley, or rye, and that when they are derived from wheat, barley, or rye, inactive ingredients are processed in a way that removes or reduces gluten to levels below 20 ppm. Similarly, the CPHA indicated that inactive ingredients derived from wheat, barley, or rye are processed in ways that remove or reduce gluten to an insignificant level and that amounts of gluten in finished nonprescription drug products is "minute, especially when compared to intake via the food supply."

FDA took these comments into account when responding to the previous petition and when developing our current approach to gluten in drug products. Both IPEC and CPHA submitted relatively brief (two-page) comments. FDA agreed with IPEC's and CPHA's overall assessments that finished drug products contain very little gluten, if any, but the Agency also noted that inactive ingredients such as wheat starch may contain more than 20 ppm gluten according to the published reports referenced in section II.E of this letter. Furthermore, these two organizations do not represent the entire pharmaceutical industry.

FDA adopted the approach described in section I.C of this letter and reflected in the Agency's draft guidance for several reasons. Notably, we determined that mandating label statements cautioning consumers that an oral drug product contains gluten, where based on the potential presence of very small amounts of gluten, would not be consistent with our approach to voluntary gluten-free labeling on foods. We did not want individuals with celiac disease to avoid taking any needed medication due to such label statements triggered by microgram quantities of gluten (as advocated in your Petition). Given our estimates that the amount of gluten potentially present in oral drug products would be very low, if present at all, we also did not want to mandate a new regulatory burden on drug manufacturers and suppliers of their ingredients, for example to require universal analytical testing to verify compliance, new product specifications,

[30] See Akobeng and Thomas, "Systematic Review: Tolerable Amount of Gluten for People With Coeliac Disease," *Aliment Pharmacol Ther 27* (February 2008); 1044-1052.

[31] See La Vieille, Dubois, et al. 2014; Catassi, Fabiani, et al. 2007.

and labeling revisions in some cases—and we did not want to commit our resources to a rulemaking, all with an unclear public health benefit.

There is no requirement for FDA to issue a rulemaking regarding the potential presence of gluten in drugs, and thus your request is to undertake one of many activities within FDA's discretion. FDA has limited resources and a large public health mandate.[32] Here, as in general, the agency evaluates options in terms of the extent of a potential risk, the time and delay that would accompany these actions, and the availability of other means to address concerns.

O. NFCA Testing

As stated above, we reviewed public comments submitted to the docket for this Petition. One comment, identified with Document ID number FDA-2015-P-5081-0020, questioned a study referenced in our previous petition response in which finished drug products were tested for gluten. This study was organized by the National Foundation for Celiac Awareness (NFCA)[33] and supported by a grant from FDA. Although this study did not feature prominently in our analysis, we described it in footnote 39 in our previous petition response as follows:

> Of the 39 drugs tested, the NFCA reported that 3 drugs tested positive for gluten in one test and none tested positive for gluten in another test. Without commenting in detail on the NFCA study, we note that the highest result the NFCA reported, 0.077 mg gluten in a unit dose, is consistent with the analysis we present in this letter and is a small fraction of the amount of gluten that may be present in a single cookie properly labeled *gluten-free* (e.g., up to 0.6 mg gluten in a 30-gram serving of food). We recognize that there are challenges associated with analytical testing of finished drug products for gluten and would welcome additional research in this area.

Soon after we issued our previous petition response, the NFCA published a revised study report, dated May 20, 2015. In its revised report, the highest of the three test results the NFCA reported as positive was now described as 77 ppm gluten in the drug product, rather than 0.077 mg per unit dose, as reported in the original September 24, 2014, study report. We noticed this discrepancy between the original and revised study reports. We determined, however, that whether the result in question should have been reported as 0.077 mg per unit dose or 77 ppm, this information did not call into question our estimates regarding the maximum levels at which gluten is reasonably expected to be found in finished drug products. If the drug product in question were a large oral dosage form (1 gram), 77 ppm would correspond to 0.077 mg. If, more likely, the drug product in question were a more typically sized oral dosage form, the quantity of gluten per unit dose would be less than 0.077 mg — in either case, well below the

[32] FDA regulates products including foods, drugs, biologics, medical devices, radiation-emitting products, dietary supplements, veterinary medicines, and tobacco products. Indeed, United States consumers spend twenty-five cents of every consumer dollar on products regulated by FDA. Given the scope of FDA's responsibilities, the agency must make difficult choices regarding how to use its limited resources.

[33] In December 2015, the NFCA changed its name to Beyond Celiac.

maximum 0.5 mg gluten we estimate that an ingredient derived from wheat, barley, or rye might contribute to a unit dose of an oral drug product.

More importantly, we have not relied on the NFCA study in formulating our current approach to gluten in drug products. As described above and in our previous petition response, our estimate that inactive ingredients will not contribute more than 0.5 mg gluten to a unit dose of an oral drug product is based on compendial specifications limiting total protein and on published reports concerning the gluten content of individual ingredients. It is not based on analytical testing of finished drug products.

III. Conclusion

Once again, we appreciate your interest in this subject and the effort you have taken to improve the welfare of individuals with celiac disease. As stated in our draft guidance, we understand that even if gluten is not present in a drug product at levels that would harm a typical individual with celiac disease, that individual may be harmed through uncertainty and lack of information. We are hopeful that our draft guidance and educational efforts will help address this problem.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

cc: Robert Vogel
Karen Bazlen
Diane Craig
Jessica Denning
Laurie Willson
Melanie Weir
Susan Larock

Gluten in Drug Products and Associated Labeling Recommendations

Guidance for Industry

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit electronic comments to https://www.regulations.gov. Submit written comments to the Dockets Management Staff (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

For questions regarding this draft document, contact (CDER) Marci Kiester 301-796-0600, or (CBER) Office of Communication, Outreach and Development, 800-835-4709 or 240-402-8010.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2017
Labeling

Gluten in Drug Products and Associated Labeling Recommendations

Guidance for Industry

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Food and Drug Administration
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Silver Spring, MD 20993-0002
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U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

December 2017
Labeling

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Gluten in Drug Products and Associated Labeling Recommendations Guidance for Industry[1]

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA staff responsible for this guidance as listed on the title page.

I. INTRODUCTION

This guidance is intended to convey to drug manufacturers FDA's recommendations on how certain drug products should be labeled regarding gluten, a matter of interest to individuals with celiac disease. Some individuals with celiac disease have faced difficulty when trying to determine whether specific drug products contain gluten. Confronted by uncertainty, some patients may forego important medication rather than risk an adverse reaction to gluten. Thus, even if gluten is not present at levels that would harm a typical individual with celiac disease, that individual may be harmed through uncertainty and lack of information.

Celiac disease (also known as celiac sprue) is an immune-based reaction to dietary gluten that primarily affects the small intestine in susceptible individuals; unmanaged celiac disease can lead to serious health complications. Approximately 1 percent of the U.S. population has celiac disease (Binder 2015). It is characterized by ongoing inflammation of part of the lining of the small intestine that generally heals if foods containing gluten are excluded from the diet and returns if they are reintroduced. At this time, the treatment for celiac disease is adherence to a gluten-free diet.

FDA's food labeling regulations define *gluten* as "proteins that naturally occur in [wheat, barley, and rye or their crossbred hybrids] and that may cause adverse health effects in persons with celiac disease (e.g., prolamins and glutelins)" (21 CFR 101.91(a)). Consistent with this definition, the term *gluten* in this document refers to certain proteins found in wheat, barley, and rye or their crossbred hybrids that lead to symptoms associated with celiac disease.

This guidance pertains to human drug products that pass through the small intestine:

[1] This guidance has been prepared by the Center for Drug Evaluation and Research in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

- Orally ingested drug products.[2]

- Topical drug products applied to or near the lips (e.g., lip sunscreens).[3]

- Drug products applied inside the mouth (e.g., cold sore treatments, drugs delivered to or via the oral cavity).

In this guidance, *oral drug product* refers to this group of products. Gluten is not believed to harm individuals with celiac disease through routes of exposure other than oral or enteral ingestion.

This guidance was developed with celiac disease in mind. However, the recommendations in this guidance may be of interest to patients with other conditions that are treated with a gluten-free diet.

This guidance does not apply to food (including dietary supplements) or products regulated solely as cosmetics.[4] In addition, this guidance does not discuss labeling recommendations regarding wheat hypersensitivity.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. DISCUSSION

A. Possible Sources and Amounts of Gluten in Oral Drug Products

Wheat is not used to a significant extent in the production of drug ingredients, and barley and rye are used either rarely or not at all.

1. Wheat Gluten as an Ingredient

Wheat gluten itself is never or very rarely added as an inactive ingredient to oral drug products during manufacture.[5] As discussed in section II.B of this guidance, any oral drug product that

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[2] The term *drug products* includes drugs subject to licensing as biological products.

[3] This includes topical drug products that are also cosmetics, such as lipsticks that are also sunscreens.

[4] For regulations pertaining to "gluten-free" labeling of foods, see 21 CFR 101.91.

[5] In this guidance, when we say *added as an ingredient*, we are referring to the intentional and purposeful addition of that ingredient. We are not referring to the introduction of wheat gluten, for example, as an unintended contaminant or impurity associated with an ingredient. Based on information available to us during our analyses for this guidance, we are aware of no oral drug products currently marketed in the United States that contain wheat gluten intentionally added as an inactive ingredient.

contains wheat gluten as an intentionally added ingredient should be labeled to indicate its presence.

Although the use of wheat gluten as an inactive ingredient in drug products does not generally mean that the product will fail to satisfy applicable requirements for safety, we may question the addition of wheat gluten to certain oral drug products on a case-by-case basis. We would be more likely to question the use of wheat gluten as an ingredient in an oral drug product for which few or no alternative treatments are available. We would also be more likely to question its use as an ingredient in an oral drug product intended for long-term administration or intended to treat comorbidities of celiac disease.

The level at which wheat gluten would be present in an oral drug product—if added as an ingredient—is directly controlled by the drug manufacturer. In the absence of more detailed information regarding wheat gluten amounts, individuals with celiac disease may choose to avoid oral drug products that are labeled as containing wheat gluten as an ingredient.

2. Wheat Gluten as an Impurity in Ingredients Derived From Wheat

Apart from its possible addition to oral drug products as an inactive ingredient—something that rarely, if ever, occurs—wheat gluten may be present at low levels as an impurity in ingredients that are derived from wheat, such as wheat starch.

In this section, we identify drug ingredients and categories of ingredients derived or potentially derived from wheat, and we estimate how much gluten they may contribute to a unit dose of an oral drug product. In general, the quantities we estimate to be present are low and do not exceed the amounts of gluten that could be found in food products labeled gluten-free under FDA's regulations (21 CFR 101.91). We present this analysis because (1) it has informed our thinking about regulatory options associated with gluten in oral drug products, (2) we would like drug manufacturers to consider the information in this section and review the ingredients they use in their drug products, and (3) if the information or assumptions underlying our analysis are proven incorrect, we would reconsider available regulatory options.

Drug manufacturers are in the best position to review their specific formulations for oral drug products and to question their ingredient suppliers about ingredients potentially derived from wheat, purification methods, and analytical testing results. We urge manufacturers to consider gluten content when formulating products using ingredients potentially derived from wheat or wheat starch.

a. Wheat flour

We are aware that some manufacturers have reported the direct addition of wheat flour to oral drug products in the past—but only very rarely. We are not aware of an oral drug product currently being marketed in the United States that contains wheat flour as an ingredient. As discussed in section II.B of this guidance, any oral drug product that contains wheat flour as an intentionally added ingredient should be labeled to indicate its presence.

The total protein content of wheat flour is generally 13 percent, with gluten representing part of the total protein.[6] The amount of gluten present in an oral drug product to which wheat flour has been added as an ingredient would depend on how much wheat flour is used. Because use of wheat flour in any drug product is so rare, we do not have good information regarding upper, lower, and typical levels that would be present in a drug product. We believe individuals with celiac disease might choose to avoid oral drug products that are labeled as containing wheat flour in the absence of more detailed information about the drug product's gluten content.

b. Wheat starch

As with wheat gluten and wheat flour, we believe wheat starch is added to oral drug products as an ingredient only very rarely. Other sources of starch (e.g., corn, potato) are more commonly used in pharmaceutical products. As discussed in section II.B of this guidance, any oral drug product that contains wheat starch as an intentionally added ingredient should be labeled to indicate its presence.

A monograph for wheat starch in the National Formulary (NF) includes a 0.3 percent limit on total protein but does not include a limit on gluten content.[7] The gluten content will be some proportion of the total protein content. Based on published information, we understand the gluten content of wheat starch suitable for use in drug products is variable but is typically in the range of 100 to 500 mg/kg (see, e.g., Kasarda, Dupont, et al. 2008). Based on our review of drug formulation information, we expect wheat starch—in the rare cases in which it is used in oral drug products—to contribute less than 0.1 mg gluten to a unit dose of an oral drug product.

c. Ingredients derived from starch

Starch is used as a starting material for manufacturing various ingredients added to oral drug products. The starch used for this purpose is often corn or potato starch, not wheat starch. Nevertheless, we recognize that very small amounts of wheat gluten may be present in starch-derived ingredients if wheat starch is used as the starting material.

Ingredients in this category—*potentially* derived from wheat starch—include modified starch, pregelatinized starch, and sodium starch glycolate. This category also includes starch hydrolysates (e.g., maltodextrin, dextrates, dextrose, maltose, and sugar alcohols such as sorbitol, xylitol, maltitol, and mannitol) and hydrogenated starch hydrolysates (mixtures of sugar alcohols).

As with wheat starch, compendial monographs for these ingredients do not include specific limits on gluten content. We have found published reports regarding the gluten content for only a limited number of ingredients derived from wheat starch. In the absence of such specific information, we have made the conservative assumption that wheat-derived modified starches

[6] According to the International Starch Institute, the typical value of total protein in wheat flour on a dry matter basis is 13 percent. See the Institute's Technical Memorandum on Wheat Starch, available at http://www.starch.dk/isi/starch/tm33wheat.asp, accessed August 2017.

[7] NF 35 Monograph: Wheat Starch, current at the time of this publication.

(e.g., modified starch, pregelatinized starch, sodium starch glycolate), although more highly processed than wheat starch, might contain gluten at the same concentrations at which gluten might be found in wheat starch: 100–500 mg/kg. Based on published literature, we believe that starch hydrolysates and hydrogenated starch hydrolysates derived from wheat may contain up to 40 mg/kg gluten (European Food Safety Authority 2007). Based on drug formulation information, we estimate that these ingredients may contribute less than 0.5 mg gluten to a unit dose of an oral drug product.

d. Ingredients produced through fermentation

Some ingredients, including citric acid and ethanol, may be produced by fermentation, in which microorganisms feed on carbohydrates from plant sources that potentially include wheat. See, for example, 21 CFR 184.1033, which describes the production of food-grade citric acid by various methods, including fermentation. If the fermentation medium includes wheat or wheat-derived ingredients, an ingredient produced by fermentation may—depending on how it is purified—contain small amounts of gluten. Compendial monographs for these ingredients do not include gluten limits.

In some cases, an ingredient such as ethanol[8] may be purified through distillation. It is unlikely that gluten (or any protein) would be present in ethanol purified by distillation using good manufacturing practices, considering the high volatility of ethanol compared with the much lower volatility of a large molecule such as gluten.

In other cases, the ingredient is highly purified through other means. Anhydrous citric acid, USP, for example, is not less than 99.5 percent pure. We expect the presence of any residual gluten in such ingredients to be very low. Based on drug formulation information we have reviewed, we expect ingredients produced through fermentation to contribute no more than 0.5 mg gluten to a unit dose of an oral drug product.

As with all of our estimates presented above, there is some uncertainty surrounding the amount of gluten that may be present in drug ingredients produced through fermentation. A more certain estimate would require production information or analytical test results covering multiple batches of the full range of ingredients made by producers around the world. In the absence of such information, we have relied on total protein limits in compendial monographs and published reports covering certain ingredients.

e. Wheat germ oil

We are aware that wheat germ oil[9] may be used as an ingredient in certain products applied topically to the lips or skin, such as lip balms or sunscreen products. If the wheat germ oil is highly refined, it is unlikely to contain detectable amounts of gluten. Even if the oil is not highly

[8] Alcohol, USP. (USP=United States Pharmacopeia.)

[9] Sometimes identified as *Triticum vulgare* (wheat) germ oil.

refined, we believe the presence of any gluten in a product applied topically to the lips would be very low, and any oral ingestion of gluten associated with the product would be insignificant.

3. Wheat Gluten as an Adventitious Contaminant

In theory, wheat gluten that is not associated with a wheat-derived ingredient could be introduced into an oral drug product as an adventitious contaminant (e.g., as a result of contact with gluten during manufacture, processing, transportation, or storage). Although we do not have systematic data in this area, we expect that any gluten present adventitiously in oral drug products would be present only in very small amounts. In all likelihood, the amount of gluten would be below the limits of detection associated with current analytical test methods. It is also likely that the amount of gluten would be well below the levels we have estimated an inactive ingredient, such as wheat starch, could potentially contribute to an oral drug product. Current good manufacturing practice (CGMP) regulations for drug products reflect a basic obligation to prevent contamination of a drug being processed,[10] and a violation of the CGMP regulations can result in an enforcement action. FDA would consider taking action if an oral drug product were found to contain significant amounts of gluten as a contaminant.

B. Labeling

If a drug included an ingredient derived from wheat, barley, or rye, the ingredient would most likely be wheat-derived. The amount of gluten potentially contributed by a wheat-derived ingredient to a unit dose of an oral drug product (unless that ingredient is wheat gluten itself or wheat flour) is expected to be less than 0.5 mg, as a high estimate.[11] As discussed in section II.A of this guidance, most oral drug products are not expected to contain ingredients derived from wheat, barley, or rye. The likelihood of them including more than one such ingredient is even less. Thus, it is expected that the amount of gluten potentially present in a unit dose of an oral drug product is less than the amount of gluten that could potentially be found in a single serving of a cookie (30 grams) labeled *gluten-free* in accordance with FDA's regulations at 21 CFR 101.91 (if all of the criteria of that regulation are satisfied).[12] Moreover, the amount of gluten estimated to be potentially present in a unit dose of an oral drug product (less than 0.5 mg) is significantly less than the range at which gluten is estimated to be present in a gluten-free diet (5 to 50 mg) (La Vieille, Dubois, et al. 2014; Catassi, Fabiani, et al. 2007).[13] This leads FDA to conclude that individuals who respond well to a gluten-free diet are at low risk of experiencing problems as a result of the possible presence of gluten in a drug product. However, we expect

[10] See generally Current Good Manufacturing Practice for Finished Pharmaceuticals, 21 CFR part 211.

[11] Our estimate is based on assumptions regarding gluten content and ingredient usage that favor a high estimate (i.e., we considered high levels of use for each inactive ingredient potentially derived from wheat, and we considered the high end of the range at which gluten is reasonably expected to be present in each ingredient).

[12] A 30-gram serving of food, corresponding to a single cookie, for example, could contain up to 0.6 mg gluten while bearing a gluten-free statement if the criteria for the definition of *gluten-free* are satisfied. 30 grams x 20 ppm=0.6 mg. See reference amounts customarily consumed per eating occasion in FDA's food labeling regulations, 21 CFR 101.12, Table 2.

[13] We recognize that gluten-free diets may be highly variable, and individuals diagnosed with refractory celiac disease may have more restrictive diets.

that they might choose to avoid using oral drug products labeled as containing *wheat gluten* or *wheat flour* as an ingredient in the absence of more information about the product's actual gluten content.

We have also considered the potential impact on those individuals with celiac disease who take multiple oral medications each day. Considering that inactive ingredients are typically derived from sources other than wheat, and that 0.5 mg of gluten per unit dose is a high estimate for gluten in an oral drug product, we expect that an individual taking multiple drug products per day would ingest much less gluten, if any, from drugs than an individual with celiac disease adhering to a gluten-free diet may ingest from food.

Some celiac patients are more sensitive to gluten than others and do not respond well to a gluten-free diet.[14] Patients who are more sensitive to gluten will likely seek to eliminate all sources of ingested gluten, or at least minimize exposure as much as possible. In all probability, these patients are under specialized care and would avoid those rare oral drug products containing added wheat starch in addition to those containing added wheat gluten or wheat flour. Additionally, they or their caregivers would likely reach out to physicians, pharmacists, other health care providers, or drug manufacturers for information about possible inclusion of wheat-derived ingredients in their oral drug products. We encourage drug manufacturers to have accurate information on the sources of their ingredients available so they can respond to questions from the public and health care providers.

1. Ingredient Labeling: Current Regulations and Practice

As described below, drug ingredients are generally identified in labeling, but substances that are present merely as impurities generally are not.

a. Nonprescription (over-the-counter) oral drug products[15]

Nonprescription drug labels must list "the established name of each inactive ingredient" under the "Inactive ingredients" heading of the Drug Facts label, which appears on the "outside container or wrapper of the retail package, or the immediate container label if there is no outside container or wrapper."[16] This information is visible to consumers at the time of purchase.[17]

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[14] See current guidelines for the diagnosis and management of celiac disease, such as those published by the American College of Gastroenterology (Rubio-Tapia, Hill, et al. 2013).

[15] The Introduction defines *oral drug products* for the purposes of this guidance.

[16] See 21 CFR 201.66(c), 201.66(d)(8).

[17] See 21 U.S.C. 321(k), 352(c).

b. Prescription oral drug products

Although not currently mandated by FDA's regulations, manufacturers of prescription oral drug products generally provide a list of inactive ingredients in the DESCRIPTION section of the prescribing information.[18]

Drugs that are licensed biological products (i.e., they are regulated under a biologics license application (BLA)) are subject to additional labeling requirements described in 21 CFR part 610, subpart G. In particular, 21 CFR 610.61 requires identification of certain types of inactive ingredients, including preservatives, "known sensitizing substances," and "inactive ingredients when a safety factor."

We interpret the requirement that inactive ingredients be identified in the labeling of biological products "when a safety factor" as meaning that *wheat gluten* and *wheat flour* must be identified by those names if they are present in orally administered biological products.

2. Established Names

According to section 502(e)(3) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), the term *established name* means (a) the official name designated pursuant to section 508;[19] (b) if there is no such name, the title of a monograph for the ingredient in an official compendium;[20] or (c) the "common or usual name" if neither (a) nor (b) applies.

Consistent with this provision, the established name used in labeling for any wheat-derived ingredient that is the subject of a monograph in an official compendium must be the monograph title, where there is no official name designated pursuant to section 508. For example, *wheat starch* (not *starch*) is the established name by which wheat starch must be identified in drug labeling. However, the more highly processed ingredients discussed in section II.A of this guidance (ingredients derived from starch and ingredients produced by fermentation) do not include a botanical source such as wheat in the established name of the ingredient because the titles of their compendial monographs do not include this designation.

If an ingredient is not recognized in an official compendium and does not have an applicable official name designated pursuant to section 508 of the FD&C Act, then it must be identified in

[18] See 21 CFR 201.57 and 201.80. Licensed biological products that meet the statutory definition of drugs under section 201(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) are subject to the labeling requirements of part 201 (except as otherwise indicated, e.g., section 201.1(m)) and drug labeling provisions of the FD&C Act, and thus also bear labeling in Physician Labeling Rule (PLR) format or non-PLR format.

[19] We do not routinely designate official names for excipients; see 21 CFR 299.4(e).

[20] An official compendium is one cited in the FD&C Act. This includes the USP, NF, and the Homeopathic Pharmacopoeia of the United States. See section 201(g) of the FD&C Act.

labeling by its common or usual name.[21] Wheat gluten and wheat flour fall into this category, and we consider *wheat gluten* and *wheat flour* to be their appropriate common or usual names.[22]

3. Section 502(f) of the FD&C Act

Section 502(f) of the FD&C Act states that a drug "shall be deemed to be misbranded . . . unless its labeling bears . . . such adequate warnings against use in those pathological conditions . . . where its use may be dangerous to health . . . in such manner and form, as are necessary for the protection of users."

We are not aware of any currently marketed oral drug product that contains wheat gluten as an intentionally added inactive ingredient. If such a product exists, we would expect *wheat gluten* to be included in its labeled list of inactive ingredients. If the labeling fails to disclose wheat gluten as an inactive ingredient, we would consider whether the product is misbranded under section 502(f) or other authorities (e.g., 21 CFR 201.66(c)(8)) in the case of a nonprescription oral drug product).

III. RECOMMENDATIONS

We encourage drug manufacturers to have accurate information about their products' gluten content available so they can respond to questions from consumers and health care professionals. Manufacturers should pay attention to possible sources of gluten in their products, consider specifications when appropriate, and consider the impact of changes in ingredient sources or formulations on gluten content.

A. Voluntary Statements Regarding Gluten

1. Statements on Labels or in Required Labeling

We recommend that drug manufacturers that wish to make statements about gluten anywhere on oral drug product labels or in required labeling use the following statement, when it is truthful and substantiated:

Contains no ingredient made from a gluten-containing grain (wheat, barley, or rye).[23]

We would interpret such a statement to mean that the manufacturer knows that no ingredient in the product was derived directly or indirectly from wheat, barley, or rye or their crossbred hybrids. This would preclude, for example, the use of ingredients derived from wheat starch or from starch of unknown botanical origin. It would also preclude the use of ingredients produced

[21] See section 502(e)(3) of the FD&C Act.

[22] *Wheat gluten* is the name given to the ingredient in FDA's GRAS (generally recognized as safe) affirmation regulation for wheat gluten (21 CFR 184.1322). See also 21 CFR 137.105, which specifically mentions wheat flour.

[23] For the remainder of this guidance, we use the phrase *recommended labeling statement* to mean this statement or minor variations with equivalent meaning and specificity.

through a fermentation process if the fermentation medium is not known to be free of ingredients derived from wheat, barley, or rye or their crossbred hybrids. Substantiation for such a statement is discussed in section III.A.2 of this guidance.

We encourage use of this recommended labeling statement to provide health care professionals and consumers with consistent, clear, accurate, and readily understood information about the gluten content of the pharmaceutical products they use. Furthermore, this phrase allows easy searching for terms such as *gluten* and *wheat*. This recommended labeling statement does not describe a drug as *gluten-free* because we have not established criteria for gluten-free statements on oral drug products, and it may be difficult to substantiate that a drug product is free of gluten. We are not aware of analytical test methods currently validated to detect or quantify gluten in finished drug products or in drug ingredients at the low levels at which it would generally be expected to be present, if at all. Furthermore, we have not determined whether a gluten-free statement on an oral drug product should refer to an absence of intact gluten or whether such a statement should also require an absence of gluten peptides.

2. *Supporting Information*

Firms are responsible for the truthfulness of their gluten-related labeling statements and for ensuring that the information related to their oral drug products supports the use of such statements.[24] Firms should also have supporting information available, including information from ingredient suppliers about their processes and raw materials. Indeed, CGMP regulations include recordkeeping requirements encompassing information that may be relevant.[25]

For firms wishing to use the recommended labeling statement, substantiation for such a statement should include a written commitment from ingredient suppliers that, for each ingredient potentially derived from wheat, barley, rye, or their crossbred hybrids or produced through fermentation, these grains are not used in the production of the ingredient.

For statements other than the recommended labeling statement, the supporting information could vary by product. For example, firms may be able to test individual wheat-derived ingredients for the absence of nitrogen (indicating an absence of all protein, including gluten), or they may be able to provide information demonstrating that the processing of such ingredients removes the gluten. If such ingredient testing is conducted, the manufacturing records[26] must include the results of any tests and the conclusions derived from them.[27] These records must be readily available to FDA for authorized inspection.[28]

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[24] See section 502(a) of the FD&C Act (21 U.S.C. 352(a)).

[25] See, e.g., 21 CFR 210.3(b)(3), 211.180(c), 211.184(c), 211.186(b)(9), 211.194(a).

[26] In this guidance, we use *manufacturing records* as an umbrella term to refer to the records discussed in 21 CFR 211.184–211.194.

[27] See 21 CFR 211.184(b).

[28] See 21 CFR 211.180(c).

B. Submission and Adoption

1. Oral Drug Products With New or Pending Applications

An applicant submitting a new drug application (NDA), abbreviated new drug application (ANDA), or BLA that wishes to use the recommended labeling statement must ensure that its use is consistent with the information in the application related to the oral drug product ingredients.[29] We are not asking that applicants submit additional specific information to their applications, such as the supplier agreements referred to above, but applicants should ensure that such information is available. An applicant that wishes to use an alternative statement should propose in the application how it intends to support the alternative statement.

2. Oral Drug Products With Approved Applications

An NDA, ANDA, or BLA holder with an approved application who seeks to change a product formulation to make a gluten statement should refer to relevant regulations and guidance regarding submission requirements associated with the formulation changes.[30]

An NDA, ANDA, or BLA holder seeking to include the recommended labeling statement who can properly substantiate it without changes to the approved product formulation may revise labeling at any time to do so. The addition of the recommended labeling statement may then be reported in the next annual report, pursuant to 21 CFR 314.70(a)(3) and 601.12(a)(3).[31]

An NDA, ANDA, or BLA holder wishing to use an alternative statement must submit the proposed statement and information that supports its use in a prior approval supplement (PAS). The addition of an alternative statement that communicates something different from or in addition to the absence of ingredients made from gluten-containing grains (wheat, barley, or rye) requires the submission and review of data not already included in the application.[32]

Regarding labeling requirements specific to generic drugs, a firm marketing a product described in an ANDA can include either the recommended labeling statement or an alternative statement addressing gluten—even if the reference listed drug (RLD) for the product described in the ANDA does not include such a statement—as long as the submission provisions described above

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[29] See section 502(a) of the FD&C Act (21 U.S.C. 352(a)).

[30] See 21 CFR 314.70(b)(2)(i), 601.12(b)(2)(i) and relevant FDA guidance documents including *Changes to an Approved NDA or ANDA* and the *Scale-Up and Post-Approval Changes (SUPAC)* documents. We update guidances periodically. For the most recent version of a guidance, check the FDA Drugs guidance Web page at https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

[31] Under 21 CFR 314.70(b)(2)(v)(A) and 601.12(f)(1), a labeling change that does not fall into enumerated categories is to be submitted as a prior approval supplement (PAS). However, under 21 CFR 314.70(a)(3) and 601.12(a)(3), an applicant is required to make a change in accordance with a regulation or guidance that provides for a less burdensome notification of the change than a PAS. Pursuant to these regulations, we are providing that notification may be made in an annual report when labels or labeling are changed to include the recommended labeling statement, without other changes to the product.

[32] See 21 CFR 314.70(b)(2)(v)(A), 601.12(f)(1).

are satisfied and the recommended labeling statement is properly substantiated or the alternative statement is approved. Conversely, if the RLD for a product described in an ANDA includes either the recommended labeling statement or an alternative statement addressing gluten, the product described in the ANDA is not required to include such a statement in its labeling to comply with the same labeling requirement that applies to ANDAs. Although the labeling of a product described in an ANDA and its RLD must generally be the same, an exception is made for differences attributable to the products being produced or distributed by different manufacturers. Such differences may include differences in labeling to reflect permissible differences in the formulation of the drug products (such as permissible differences in inactive ingredients) and labeling revisions made to comply with current FDA labeling guidelines or other guidance. See section 505(j)(2)(A)(v) of the FD&C Act and 21 CFR 314.94(a)(8)(iv).

3. Oral Drug Products With Approved Applications That Already Include a Statement About Gluten Other Than the Recommended Labeling Statement

We are aware that some marketed oral drug products already include a gluten labeling statement other than the recommended labeling statement described in this guidance. Firms are encouraged to determine whether they will revise their labeling to use the recommended labeling statement or whether they have an adequate basis for the continued use of an alternative statement.

If a firm chooses to adopt the recommended labeling statement and this action does not require changes in the product formulation (or is not combined with another change that requires submission of a supplement), the firm may submit this labeling change in an annual report to the NDA, ANDA, or BLA (21 CFR 314.70(a)(3), 601.12(a)(3)).

However, if adopting a gluten labeling statement requires changes in the product formulation (or is combined with other labeling changes that require a PAS), the application holder must submit the change in a PAS.[33]

4. Nonapplication Oral Drug Products

For oral drug products marketed without an application, firms may revise their labeling to adopt the recommended labeling statement if the statement is truthful and substantiated.

As noted above, if an oral drug product's labeling already includes a gluten statement, firms are encouraged to review this guidance and determine whether they will revise their labeling to use the recommended labeling statement. If a firm wishes to continue to use a labeling statement other than the recommended labeling statement, the firm is responsible for the truthfulness of such a statement and for ensuring that the information related to the oral drug product supports its use.[34]

[33] See 21 CFR 314.70(b)(2)(i), 601.12(b)(2)(i).

[34] See section 502(a) of the FD&C Act (21 U.S.C. 352(a)).

C. Placement of a Voluntary Gluten Labeling Statement

1. Prescription Oral Drug Products

When used, a voluntary gluten statement should be included in the DESCRIPTION section of the prescribing information. Specifically, it should appear at the end of the inactive ingredients list. If the oral drug product has associated FDA-approved patient labeling, the statement should also appear in that patient labeling, either at the end of an inactive ingredients list or at the end of the patient labeling, after the name and address of the manufacturer, packer, or distributor. In addition, if a voluntary gluten statement is included on the immediate container label and, if applicable, carton labeling, it should appear on the side or back panel. The statement should not appear on the principal display panel, to avoid interference with the required or recommended information that appears on labels and labeling.[35]

2. Nonprescription Oral Drug Products

Voluntary gluten statements should be visible at the time of purchase and should appear on the immediate container label and carton labeling in a location outside of the Drug Facts label. The statement must not interfere with the required information that appears on labels and labeling.[36]

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[35] The prominence, placement, font, and color should be consistent with the concepts described in the draft guidance for industry *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*. When final, this guidance will represent the FDA's current thinking on this topic. See also section 502(c) of the FD&C Act (21 U.S.C. 352(c)) and 21 CFR 201.15, on prominence of required labeling information.

[36] The general labeling requirements in 21 CFR part 201 specify which information must be included on a drug product's labeling and how the information should be presented, among other things. See also section 502(c) of the FD&C Act (21 U.S.C. 352(c)) and 21 CFR 201.15, on prominence of required labeling information.

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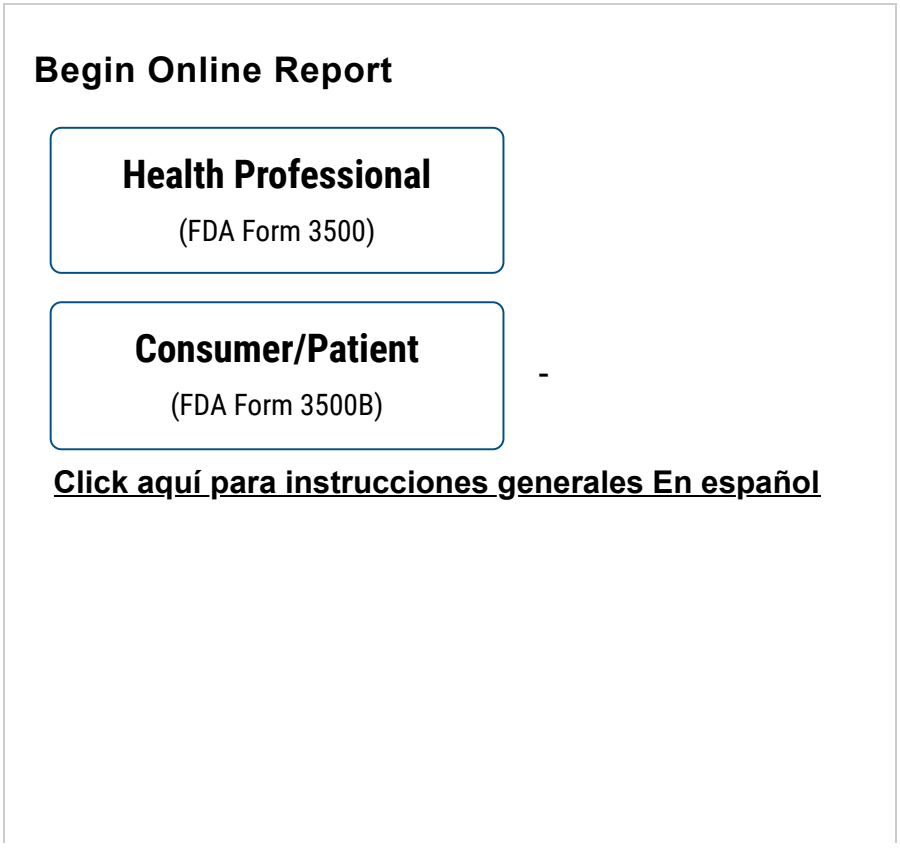

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Attention Frequent MedWatch Online Reporters:

If you maintain a Safety Database and are a frequent submitter of MedWatch Online (MWO) health care professional reports or currently fax the 3500 Form to the FDA, you may be eligible to submit reports through the MWO Application Programming Interface (API). This streamlined method is ideal for high-volume reporting and ensures faster, more secure data transmission. For more information or to get started, please review the **FAQ (index.cfm?action=reporting.faqs)** for MWO API.

Thank you for taking the time to submit a MedWatch report. If you wish to download and print a copy of your report please review the MedWatch Voluntary Report Frequently Asked Questions. (index.cfm?action=reporting.faqs)

MedWatch Online allows reporters to start a report and complete it within 3 days. Reporters can save an incomplete report and provide an email address to receive instructions on how to complete & submit a report with Report ID and Report Date.

Note that after submitting, you cannot retrieve the report and edit it. However, you can start a new report and supply more information about the case. Please include the suspect product and a brief summary of the adverse events, medical/product use errors, or product quality issues. Other information such as the reporter and the patient characteristics (if available) should also be provided again. This may appear repetitive, but it helps the FDA connect the new report with the previously submitted one.

Information You Should Report to MedWatch

- **Unexpected side effects or adverse events** can include everything from skin rashes to more serious complications.
- **Product quality problems** such as information if a product isn't working properly or if it has a defect.

- **Product Use/Medication Errors that can be prevented.** These can be caused by various issues, including choosing the wrong product because of labels or packaging that look alike or have similar brand or generic names. Mistakes also can be caused by difficulty with a device due to hard-to-read controls or displays, which may cause you to record a test result that is not correct.
- **Therapeutic failures.** These problems can include when a medical product does not seem to work as well when you switch from one generic to another.

Types of FDA Regulated Products You Can Report Through MedWatch

- **Prescription and over-the-counter medicines** including those administered in a hospital or outpatient infusion centers.
- **Biologics** such as blood components, blood/plasma derivatives, blood transfusions, gene therapies, and human cells and tissue transplants.
- **Medical devices** such as diabetes glucose-test kit, hearing aids, breast pumps, and many more products.
- **Combination products** such as prefilled drug syringe, auto-injectors, metered-dose inhalers, contact lens coated with a drug and nasal-spray.
- **Cannabinoid hemp products** such as products containing CBD.
- **Cosmetics** such as moisturizers, shampoos, conditioners, hair dyes and tattoos.

Where to Report Other FDA Regulated Product Safety Information

Other products that the FDA regulates, such as Food Products, Tobacco Products, Vaccines and Animal/Livestock medicine and feed, utilize different reporting pathways. It is recommended that reports concerning these products be submitted directly to the appropriate portals below.

- **Food or dietary supplement products:** Report problems or adverse health events and food product problems, such as beverages, ingredients added to foods, dietary supplements, medical foods, and infant formulas. Report problems to the **Safety Reporting Portal (https://www.safetyreporting.hhs.gov/SRP2/)**.
- **Tobacco, E-cigarettes or Vaping:** Report problems or adverse health events and tobacco product problems, include problems with e-cigarettes (also known as "vapes"), e-liquids, heated tobacco products, cigarettes, roll-your-own cigarettes, cigars, little cigars, pipes, waterpipes (also known as hookah), chewing tobacco, snuff, or snus. Report issues to the **Safety Reporting Portal (https://www.safetyreporting.hhs.gov/SRP2/)**.

- **Vaccines:** Report vaccine events to the Vaccine Adverse Event Reporting System (VAERS) online at **https://vaers.hhs.gov/reportevent.html. (https://vaers.hhs.gov/reportevent.html)**
- **Animal Drug, Device, Pet Food and Livestock Feed Problems (pet food and livestock feed):** For information on how to report visit **www.fda.gov/vetproductreporting. (https://www.fda.gov/vetproductreporting)**

Note that submissions for these products through MedWatch will be accepted and directed to the correct center or office.

Additional Resources ^

- **MedWatch Home (https://www.fda.gov/Safety/MedWatch/default.htm)**
- **Download Forms (https://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm)**
- **OMB Paperwork Reduction Act (index.cfm?action=reporting.OMB)**
- **Your Privacy Statement (index.cfm?action=reporting.privacy)**
- **Frequently Asked Questions (index.cfm?action=reporting.faqs)**
- **Join E-list (https://www.fda.gov/safety/medwatch-fda-safety-information-and-adverse-event-reporting-program/about-medwatch-e-list)**
- **Help (https://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/ucm149236.htm)**

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119TH CONGRESS
1ST SESSION

H. R. 3821

To amend the Federal Food, Drug, and Cosmetic Act to require the label of a drug intended for human use to identify each ingredient in such drug that is, or is derived directly or indirectly from, a major food allergen or a gluten-containing grain, and for other purposes.

IN THE HOUSE OF REPRESENTATIVES

JUNE 6, 2025

Ms. MORRISON (for herself, Mr. LAWLER, Ms. MATSUI, Mr. CLINE, Mr. FITZPATRICK, and Mr. BACON) introduced the following bill; which was referred to the Committee on Energy and Commerce

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A BILL

To amend the Federal Food, Drug, and Cosmetic Act to require the label of a drug intended for human use to identify each ingredient in such drug that is, or is derived directly or indirectly from, a major food allergen or a gluten-containing grain, and for other purposes.

Be it enacted by the Senate and House of Representatives of the United States of America in Congress assembled,

SECTION 1. SHORT TITLE.

This Act may be cited as the ''Allergen Disclosure In Non-food Articles Act'' or the ''ADINA Act''.

SEC. 2. LABELING OF DRUGS WITH AN INGREDIENT THAT IS A MAJOR FOOD ALLERGEN OR IS MADE FROM A GLUTEN-CONTAINING GRAIN.

(a) MISBRANDING.—Section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) is amended by adding at the end the following:

''(hh) If it is a drug—

''(1) that is intended for human use;

''(2) that contains an ingredient that is, or is derived directly or indirectly from—

''(A) a major food allergen; or

''(B) a gluten-containing grain (including wheat, barley, rye, and their crossbred hybrids); and

''(3) whose label fails—

''(A) to state that the drug contains such an ingredient; and

''(B) to identify each such ingredient and, as applicable, the type of gluten-containing grain.''.

(b) APPLICABILITY.—Section 502(hh) of the Federal Food, Drug, and Cosmetic Act, as added by subsection (a), shall apply beginning on the earlier of—

(1) a date to be determined by the Secretary of Health and Human Services; or

(2) the date that is 2 years after the date of the enactment of this Act.

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