Gluten in Drug Products and Associated Labeling Recommendations

Guidance for Industry

DRAFT GUIDANCE

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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This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA or Agency) on this topic.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

[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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European Food Safety Authority, 2007, Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a Request From the Commission Related to a Notification From AAC on Wheat-Based Maltodextrins Pursuant to Article 6, Paragraph 11 of Directive 2000/13/EC, The EFSA Journal, 487:1–7.

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.