American Pharmacists Association
House of Delegates – Nashville, TN

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NEW BUSINESS

(To be submitted and introduced by Delegates only)

Introduced by: Carmela Silvestri PharmD
(Name)

2/13/2018 **(Date)**

New Jersey Pharmacists Association **(Organization)**

Subject: Gluten Content and Labeling in Medications

Motion: Move to adopt the following policy statements:

1. APhA supports labeling of all prescription and over the counter medications that indicates the presence or absence of gluten (protein associated with wheat, barley, rye or their derivatives) regardless of whether the addition of these substances is intentional or inadvertent.
2. APhA supports required gluten status verification for all plant derived excipients used in the manufacture of medications to assure that no cross-contamination has occurred, and in the absence of this verification, that batch testing of medication products be required to determine if they are free of detectable gluten.
3. APhA encourages the FDA to require post manufacturing testing of gluten content in oral drug products, and making quantitative information on gluten content easily accessible to health professionals.
4. APhA encourages USP to develop assays that can accurately detect trace levels of gluten in finished drug products and set appropriate standards
5. APhA encourages manufacturers to formulate drug products without use of wheat, barley, rye or their derivatives whenever possible.
6. APhA supports a mechanism for third party payers to acknowledge the need for, and accept responsibility for providing access to, medications with no detectable gluten when medically necessary.
7. APhA supports additional research on the effects of gluten intolerance and celiac malabsorption, particularly as it relates to medication absorption.
8. APhA supports pharmacist education regarding celiac disease and non-celiac gluten sensitivity.

Background:

Supporting statements

1. Several studies have been done to estimate the time required by pharmacists in determining the gluten status in medications in order to protect patients from exposure. The celiac community is riddled with anecdotal stories of patients who report being left to check with manufacturers on their own to verify gluten status of their

medications. This is presumably because of the uncompensated time burden on pharmacies associated with calling manufacturers with each prescription to determine gluten content. To compound the problem, not all drug manufacturers are able to provide information on excipients and those who can, may change their sources at any time -without informing the patient or pharmacy. Manufacturer information contacts are not available during all pharmacy hours when this information is needed. Drug product information specialists may need to research the gluten status before responding. Ingredients derived from wheat, barley or rye include Modified starch (source not specified), Pregelatinized starch (source not specified), Pregelatinized modified starch (source not specified), Dextrates (source not specified), Dextrin (source not specified but usually corn or potato), Dextrimaltose (when barley malt is used), Caramel coloring (when barley malt is used). Pharmacists may not recognize these as gluten sources. Frequently the response from manufacturers is that no gluten containing ingredients are used in the manufacturing process but that the company acknowledges that they cannot verify that the final product is gluten free.

2. It is generally accepted that grains such as oats and dried legumes are subject to cross contamination as a result of crop rotation, farming equipment and shared processing facilities. Untested foods, which would normally be considered allergen free, are frequently labeled to inform more sensitive consumers of the risk of cross contamination. These labels may take the form of the statement: "made in a facility that also processes wheat". This labeling is voluntary in the Food Allergen Labeling and Consumer Protection Act (FALCPA). This information would be useful in excipients used in production of medications as it would indicate a need for additional determination of purity. Although use of GMPs may preclude contamination in the drug manufacturing process, this is not the case for excipients processed as foods (for which labeling of gluten content is voluntary).
3. Symptoms associated with celiac disease may be intestinal or extra-intestinal. Clinical intestinal symptoms include diarrhea, flatulence, severe stomach pain, weakness and fatigue. Extra intestinal symptoms are multi-systemic and may include neurologic symptoms such as paresthesia, migraine, and seizure and hormonal abnormalities such as amenorrhea, infertility and impotence. Continued exposure can lead to osteopenia, anemia, prothrombin deficiency, failure to thrive and growth retardation associated with malabsorption syndrome. An increased risk of gastric malignancies and B- Cell and T-cell lymphoma is seen. Research has shown that the threshold for symptoms resulting from gluten exposure is subject to significant patient variability. It is important to note that it has been estimated that up to 70% of patients with celiac disease do not report any clinical symptoms. These asymptomatic patients have no outward signs to indicate they have experienced stimulation of the autoimmune response and will experience disease-associated intestinal damage with continued exposure. In addition, up to 6 percent of the population suffers from non-celiac gluten sensitivity (NCGS) resulting in varying degrees of clinical illness as a result of gluten exposure without evidence of intestinal autoimmune damage. Standards for labeling of finished products would guarantee that patients are not exposed without their knowledge. If all products are tested, the noting of the presence of detectable gluten content on labels would allow patients, along with their pharmacist/physician, to evaluate the risk/benefit of treatment. Easily retrievable information on gluten content in products would allow a pharmacist to identify products with lower content when trace gluten exposure cannot be avoided.
4. The definition of the terminology "gluten free" was regulated in food products in 2014 as a voluntary labeling standard. The standard of 20ppm was chosen as the lowest level detectable using available technology at that time. It is now possible through Elisa testing to determine levels of intact proteins as low as 5ppm and protein fragments at 10ppm. Studies are needed to determine if peptide fragments with single receptor sites can cause as much damage as complete proteins. The Health Hazard Assessment for Gluten Exposure in Individuals with Celiac Disease: Determination of Tolerable Daily Intake Levels and Levels of Concern for Gluten (May 2011) conducted by Office of Food Safety Center of Food Safety and Applied Nutrition Food and Drug Administration stated that repeated (sub-chronic) exposure of 0.4mg/day of gluten was shown to produce morphological changes in diagnosed celiac patients. FDA also determined in this report that a single exposure of 0.015mg could cause clinical symptoms in patients. Establishment of any "acceptable" gluten level in medications would need to account for regimens that require ingestion of multiple units such as dosing of 3-4 dosage units per day, as well as, the combined effect of multiple medications used in combination to treat one or more chronic disease. To

eliminate the risk of medications causing damage to susceptible patients, gluten content may need <1ppm. Since we do not currently have an assay designed for drug testing to determine trace amounts, we feel that APhA should encourage USP to develop testing methods that would allow the industry standard to be established at a level that would truly protect these patients.

5. An obvious solution to the problem of gluten exposure is the elimination of known sources of gluten that cannot be refined to a level that would be safe. Encouraging manufacturers to eliminate these excipients in their products moving forward would be helpful. Full disclosure of the inclusion of any known gluten source is essential to patient safety but currently not regulated.
6. Celiac patients who experience clinical adverse effects from a gluten contaminated medication product may either incorrectly attribute the symptoms to the active drug ingredient (assuming the medication to be unacceptable) or refuse treatment altogether. Treatment refusal can lead to worsening disease, hospitalization and additional cost and adverse effects on quality of life. Since complete abstinence from ingested gluten is the only treatment for celiac disease, third party payers need to bear the responsibility for ensuring that medication used to treat a different illness does not aggravate celiac autoimmune disease.
7. Celiac disease related malabsorption could necessitate changes in oral dosing, and adjustment as intestinal healing occurs. Research into the implications of the effects on medication absorption could allow pharmacists and prescribers to better manage these patients.
8. Pharmacists need to be aware of celiac disease and gluten sensitivity in order to guide patients to verified gluten-free products and assist in limiting inadvertent exposure.

Why this is important?

Approximately 1% of the population or 3 million Americans have celiac disease. Celiac disease is diagnosed endoscopically when changes in intestinal morphology due to inflammatory autoimmune damage are found. These changes are the result of exposure to gluten, which is defined as the proteins found in wheat, barley, rye, and most of their derivatives. Although celiac autoimmune stimulation has been known to result in multisystem damage, no absolute safe threshold for stimulation of the autoimmune response has been established due to heightened sensitivity in some patients. Some celiac patients may be unable to tolerate even trace exposure.

The estimate of 3 million people with celiac disease in the US may be conservative. Less than half experience the clinical symptoms that would cause them to seek a diagnosis until malabsorption complications are experienced. Asymptomatic patients are diagnosed based on family screening and based on results of endoscopy performed for other reasons. Celiac related malabsorption has been linked to several forms of anemia, vitamin K deficiency coagulation abnormalities, osteopenia, and growth disruption, weight loss and failure to thrive in children. The genetic predisposition is shared by 40% of the general population and is common to all celiac patients, but the trigger to active disease is still subject to speculation. The medical community is slow to suspect celiac disease in adult patients and it takes an average of 4-8 symptomatic years before being correctly diagnosed.

In 2011, the Health Hazard Assessment for Gluten Exposure in Individuals with Celiac Disease: Determination of Tolerable Daily Intake Levels and Levels of Concern for Gluten (May 2011) conducted by Office of Food Safety Center of Food Safety and Applied Nutrition Food and Drug Administration showed that adverse changes in intestinal morphology were detected with exposure to 0.4mg/day. Clinical patient specific symptoms were observed with exposure to 0.015mg. Morphological changes are associated with complications such as lymphoma and gastric carcinoma. Clinical symptoms are varied but include intestinal symptoms such as severe stomach pain, nausea and diarrhea. Extra-intestinal symptoms are varied and include dermatologic (rash) , neurologic(headache including migraine, brain fog, learning disability and seizure) and musculoskeletal symptoms such as myalgia and fatigue. Although the hazard study was limited to patients with celiac disease, up to 6% of the population may suffer from non-celiac gluten sensitivity (NCGS)resulting in varying degrees of clinical illness as a result of exposure.

As a result of the existing evidence, FDA established guidelines for the voluntary labeling of food products as "gluten free", the threshold of 20ppm was established as the standardized criteria for this designation. Although

some patients experience clinical symptoms below this threshold, this served as a guide to patients that labeled products are produced with an effort to minimize contamination and are tested for gluten content when the risk exists. It is important to recognize that patients who experience symptoms when consuming a food can make the choice to no longer purchase and consume the offending product. A medication needs to be taken on schedule for the prescribed course. Sometimes this schedule involves up to 4 or more dosage units every day. Currently, insurance does not cover the filling of more than one prescription in a specific period, all but eliminating the option to try a product from a different manufacturer. Insurance coverage may require prohibitive copays for the branded drug or more expensive generic products that may not produce the symptoms. In many cases the only option is to consider the medication a failure, and obtain a prescription for a different treatment.

Currently, the only known treatment for celiac disease is strict adherence to a gluten free diet. A prescription requiring "Gluten Free" product is meaningless if products have not been proven and labeled to be gluten free.

Few products are formulated with gluten containing ingredients listed below*. In a January 2018 article by Shah in the Journal of Pharmaceutical Sciences titled: Making All Medications Gluten Free, replacing all gluten containing starch derivatives with alternatives is explored as a way of eliminating the risk of gluten exposure. Current good manufacturing practices (cGMPs) make contamination during manufacturing highly unlikely. Unfortunately, there is no current requirement that raw materials used as inactive ingredients in medication manufacturing be tested, and proven free of gluten contamination. Without assuring that the ingredients themselves are certified to be free of gluten the risk of contamination remains. For this reason, pharmacists, and sometimes patients, who call a drug manufacturer, are often told that their product "contains no gluten containing ingredients". They are unable to state that the finished product is gluten free because gluten contamination is not included in post-production batch testing. For food, the product must either have no risk of contamination based on the content and manufacturing process or that batch test results are less than 20ppm in order to be labeled "Gluten Free".

Labeling of GF for products with gluten content below 20ppm is voluntary in food products (which may be avoided by choice in highly sensitive patients who experience adverse clinical effects). We believe that standards stringent enough to eliminate the risk of symptoms for most celiac patients (0.015mg of daily exposure at standard dosing) should be imposed on all drug products in the interest of patient safety. Any product that is not certified at this level of purity should be labeled differently than those that can verify purity. No one should refuse their medications based on fear of undisclosed gluten contamination. In 2014 the National Foundation for Celiac Awareness conducted a study resulting in a report, "Gluten in Medication: Qualifying the Extent of Exposure to People with Celiac Disease and Identifying a Hidden and Preventable Cause of an Adverse Drug Event". The study collected reports of celiac patients who experienced symptoms consistent with gluten exposure while taking medications. A number of these medications were tested for gluten content using the most sensitive tests available. Gluten contamination above the 20ppm threshold for gluten free food was identified in some of the reported products even though the manufacturers had stated that they were made without gluten containing ingredients.

As the elimination of even the smallest amount of gluten is the current treatment plan for millions of Americans, identifying presence or absence of gluten and labeling this on drug products should be a part of drug safety standards. Products using excipients with any risk of contamination through processing should be flagged so that the patient along with their pharmacist can determine the risk/benefit of use. Quantitative assessment of any known gluten content should ALWAYS be available on request in order to help pharmacists assist with product selection.

Why now?

In December the FDA posted proposed Gluten in Drug Products and Associated Labeling Recommendations Guidance for Industry-. Comments were received until February 12th, 2018. NJPhA believes that the APhA should take a stand on labeling of gluten in medications in order to protect patients this year while FDA is considering options for dealing with the problem. It is essential that pharmacists be educated on the disease state and demand the information needed to care for these patients.

References:

* Shah A.V, Serajuddin ATM, Mangione RAl. Making All Medications Gluten Free. Journal of Pharmaceutical Sciences xxx (2018) 1-6
Health Hazard Assessment for Gluten Exposure in Individuals with Celiac Disease: Determination of Tolerable Daily Intake Levels and Levels of Concern for Gluten. Office of Food Safety-Center of Food Safety and Applied Nutrition Food and Drug Administration-May 2011

Magione et al. Determining the gluten content of nonprescription drugs: Information for patients with celiac disease Journal of Pharmaceutical Sciences. 2011:51:734-737

Kelly CP et al. Advances in Diagnosis and management of Celiac Disease. Gastroenterology. 2015 May ; 148(6): 1175–1186.

Ross M. Gluten Content of Top 200 Drugs: Key Information for Pharmacists. Pharmacy Times. June 9, 2016 accessed at: http://www.pharmacytimes.com/news/gluten-content-of-top-200-drugs-key-information-for-pharmacists

Celiac Disease Facts and Figures. The University of Chicago Medicine Celiac Disease Center at: https://www.cureceliacdisease.org/wp-content/uploads/341_CDCFactSheets8_FactsFigures.pdf

Gluten in medication: Qualifying the Extent of exposure to people with celiac disease and identifying a hidden and preventable cause of an adverse drug event" by NFCA
(Robert Mangione-Chief investigator)

Choung RS,Murray JA. The US Preventive Services Task Force Recommendations on Screening for Asymptomatic Celiac Disease:A Dearth of Evidence. JAMA. 317 (12) March 2017

Other information:

*Ingredients which can be derived from a gluten containing grain:

Wheat, barley or rye may be the source of a limited number of excipients. Examining a medication's inactive ingredient list for a red-flag ingredient is the only way that people following a medically necessary gluten-free diet and their healthcare providers have to assess for gluten in a drug. The following inactive ingredients may be sourced from wheat, barley or rye:

- Wheat
- Modified starch (source not specified)
- Pregelatinized starch (source not specified)
- Pregelatinized modified starch (source not specified)
- Dextrates (source not specified)
- Dextrin (source not specified but usually corn or potato)
- Dextrimaltose (when barley malt is used)
- Caramel coloring (when barley malt is used)

Historical Timeline of Progress in Gluten Labeling of Medications

2008-Private citizen submits a petition to the FDA requesting regulation specifying that no medication, either prescription or OTC, contain wheat gluten as an ingredient, and if this is refused that this ingredient be made known.

2011- Federal Register includes discussion of gluten hazard study: "Based on this health hazard assessment, a conservative tolerable daily intake level for gluten in individuals with celiac disease is 0.4 milligrams (mg) gluten per day for adverse morphological effects and 0.015 mg gluten per day for adverse clinical effects".

2013- FDA enacts regulation governing the voluntary use if the term "gluten free" to specify finished food products that will test at <20ppm of gluten. Manufacturers had until August 2014 to comply

2014-September- Results of "Gluten in Medication: Qualifying the Extent of Exposure to People with Celiac Disease and Iidentifying aHidden and Preventable Cause of an Adverse Drug Event" by NFCA(Robert Mangione-Chief investigator)

2015- May 12, 2015-FDA responds to citizen petition labeling; request denied because: "Based on drugformulation information, we estimate that these ingredients may contribute no more than 0.5 mg gluten to a unit dose of an oral drug product."

2015-September-Representatives Tim Ryan (OH-13) and Nita Lowey (NY-17) introduce the Gluten in Medicine Identification Act to Congress

2015-The FDA responds to the citizen petition which is made public by the recipient that guidance for labeling will be forthcoming.

2017-December- FDA published Gluten in Drug Products and Associated Labeling Recommendations Guidance for Industry in the Federal Register with a comment period opened until Feb 12th 2018

2018-March APhA considers gluten content labeling in the House of Delegates.

Current APhA Policy & Bylaws:

2004, 1970 Disclosure of Ingredients in Drug Products

APhA supports legislation or regulation to require a full disclosure of therapeutically inactive, as well as active ingredients of all drug products.

(JAPhA NS10:357 June 1970) (JAPhA NS44(5):551 September/October 2004) (Reviewed 2010) (Reviewed 2015)

****Phone numbers will only be used by the New Business Review Committee in case there are questions for the delegate who submitted the New Business Item Content.**

New Business Items are due to the Speaker of the House by **February 14, 2018** (30 days prior to the start of the first House session). Consideration of urgent items can be presented with a suspension of the House Rules at the session where New Business will be acted upon. Please submit New Business Items to the Speaker of the House via email at hod@aphanet.org.