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

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Abstract:

Approximately two to three million people with celiac disease and millions more with non-celiac gluten sensitivity (NCGS) are unable to safely consume gluten, the protein in wheat, barley and rye. Although relatively few medications contain gluten, every medication must be investigated to verify its gluten-free status since labeling regulations do not currently exist. This preliminary research is intended to inform stakeholders about the possible impact of adverse drug events due to unlabeled gluten in prescription (Rx) and over-the-counter (OTC) medications for those following a medically required gluten-free diet.

This study is not intended to identify specific drugs that contain gluten but, rather, to determine if gluten in medication is a matter of concern for the gluten-free population. Its purpose is to better understand *the circumstances* that may lead to gluten in medication causing an adverse drug event. Further, it is intended as a foundation study from which further investigation will bring more complete understanding of the scope of this issue. As a result, the report focuses on the causes of the adverse events, and not the testing results. The names of the manufacturers of the drug products that tested positive are not identified.

The National Foundation for Celiac Awareness (NFCA), the institution that received the grant to support this study, and other celiac disease stakeholders distributed an electronic and print survey to people with celiac disease and NCGS in the US in order to better understand their experiences securing and taking drugs. Demographic information was collected and responses were analyzed. Subjects named 242 different drugs suspected of causing a gluten-related reaction. Of the 242 drugs, 39 drugs were tested: the seven most frequently reported OTC and eight Rx drugs were tested, along with 24 other medications. Herbal supplements, topical formulations and injections were excluded from the study.

Two assays were used to quantify gluten in the medicines: R-Biopharm's Competitive ELISA tests for hydrolyzed product and measures at a level of quantification (LOQ) of 10 parts per million (ppm) while its Sandwich ELISA measures gluten at a LOQ of 5 ppm. None of the medications tested above the LOQ on the Sandwich ELISA and three medications tested over the LOQ on the Competitive ELISA.

The study yielded some anticipated and some surprising results. As expected, the study confirmed that the celiac disease and NCGS patient populations experienced adverse drug events due to an inability to accurately ascertain if gluten is an ingredient of ingested medicines. This resulted in changing therapeutic regimens to second tier treatments and consumers changing their purchasing decisions which also impacts the marketplace.

We encourage collaboration between stakeholders to satisfy the need for clarity on medication labels and package inserts. We also recommend further research to be built upon the foundation of this study to assist in safely meeting the needs of these populations.

The research team had some testing difficulties due to the small size of each dosage form. This suggests that future research of various testing methods for the presence of gluten in drugs is needed. The study was not intended to show a cause and effect of the alleged gluten reactions; this may be another area for further exploration.

Objective:

Our goals were to characterize the problem of unlabeled gluten in medication and to determine the levels of gluten in identified drugs that were reported by celiac disease and NCGS patients to have caused them adverse reactions that they associated with unlabeled gluten in the product.

- To address the problem of unlabeled gluten in medication: Current US Food and Drug Administration (FDA) regulations do not require that the source of excipients (inactive ingredients) in medications be identified. Wheat, a common source of gluten, is sometimes a component of excipients and is harmful to people with celiac disease.

- To raise awareness of the potential harm that can occur to patients who ingest medications that they do not recognize contain gluten, and to serve as a foundation study for future research: Patient reports indicate that gluten in medication is problematic. Prior to this research, specific studies addressing this concern were lacking.

Introduction:

An estimated two to three million Americans[1] [2] have celiac disease, a genetically based autoimmune digestive disease. The only treatment is a lifelong gluten-free diet.[3] Millions more Americans have NCGS[4] and also refrain from ingesting gluten. Gluten, a protein in wheat, barley and rye, is deleterious to these populations. Manifestations of ingested gluten are varied and may impact every system of the body: Gastrointestinal problems, neurological disorders, reproductive system problems and malignancies are among the myriad signs and symptoms of this disease.

Since gluten-derived ingredients may be used as excipients in the formulation of medication, understanding and identifying the preventable harm from gluten in medication is imperative for the drugs' safe use by this large patient population.[5] The number of people with celiac disease has increased 400% in the past 50 years,[6] dramatically raising the public health risk.

While the FDA defined *gluten-free* in August 2013, the rule applies to voluntary labeling for food and dietary supplements. Despite this recent success in the food industry, the rule does not impact the labeling of drugs. There are no US regulations requiring or guiding manufacturers on how to specify if gluten is present in medication.

Prior to embarking on this study, the National Foundation for Celiac Awareness (NFCA) was alerted to numerous anecdotal reports of patients experiencing adverse effects from medication in which gluten was suspected as the cause. Healthcare providers and pharmacists also expressed frustration at their inability to consistently and readily ascertain if a needed medicine contained gluten. NFCA received one report of a pharmacy refusing to serve a patient because it feared legal liability if a dispensed drug did contain gluten.

Respondents to the *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* survey indicated that survey participants experienced adverse drug events, and they believe that gluten was the cause. The qualified findings of the survey, coupled with the testing of a select number of drugs identified by survey respondents, provide the preliminary basis for further study in this

area. It is expected that findings from this research study will drive future studies toward human clinical research to support additional root cause analysis.

Study findings indicate two key areas for further activity and research:

1. Labeling: The FDA Safe Use Initiative has repeatedly requested scientific data to support the need for labeling of gluten in medication. Although preliminary, this research began the process of advancing knowledge in this area from anecdotal patient reports to a scientifically valid and trusted body of data. With this information, we hope that the FDA's Safe Use Team will be able to move forward to address this area of preventable harm.
2. Research: The findings of this preliminary study identified the need for additional research in the area of gluten in medication: human clinical research on the effects of gluten in medication when ingested by people with celiac disease. Subsequent research projects may involve controlled studies that include pre and post-test biopsies of human subjects exposed to the medications that are identified in this study.

Background

In this study, we use the term *adverse drug event* as defined by the FDA: "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."[7]

The FDA also defines a *suspected adverse reaction* as: "any adverse event for which there is a reasonable possibility that the drug caused the adverse event. … Suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug."[8]

Based on these definitions, harm that befalls an individual because of unlabeled gluten in the medication is considered an adverse drug event.

The Problem: Patient Reports

There have been many anecdotal cases of people with celiac disease having adverse reactions to gluten in medication. As we consider the various reports, it is worth noting that the preventable harm may be a direct effect of the gluten in the drug (physical harm), or a result of additional diagnostic procedures, changes in the therapeutic regimen and other modifications of therapy that may not have been needed (physical harm). The patient's confidence in the medication therapy and their healthcare provider may also be compromised (psychological harm).

The Problem: Pharmacists' Dilemma

Although relatively few medications contain gluten, every medication must be investigated to verify its gluten-free status since labeling regulations do not currently exist. Currently, pharmacists and patients must explore the ingredients of each medication or contact the manufacturers to ask if the required medication contains gluten. Answers are not available after regular business hours, and sometimes manufacturers are not prepared with the responses when contacted during the day. Further, the formulations may change after investigation,

rendering each inquiry valid only for that specific timeframe. Attempts have been made to develop consumer-driven lists of gluten-free medication, but these require constant updating and oftentimes contain errors.[9] [10]

The following inactive ingredients are considered "red flags," as they may be sourced from wheat, barley or rye. The presence of red-flag ingredients indicates that there is a need for additional investigation to determine if the drug's ingredients were derived from gluten:[11]

- 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)

The Problem: Labeling

In the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA), Congress recognized celiac disease as a multi-system disease affecting one percent of the US population that must be treated with a gluten-free diet, and it ordered the FDA to define gluten-free.[12] In response, on August 2, 2013, the FDA announced to the public its Final Rule defining gluten-free for food products. In its most basic sense, a packaged food product regulated by the FDA that is labeled gluten-free must contain less than 20 ppm gluten, and it must also comply with additional criteria beyond this specific threshold.[13]

Through the FALCPA process, the FDA received some comments about gluten in drugs. To better understand this area, the FDA published an invitation on December 21, 2011 for public comment about drug ingredients that are derived from wheat, barley or rye, and for information about ways to help people with celiac disease avoid gluten in medicine, if it was contained in the oral dosage form. The notice also sought information from manufacturers about medicines that have ingredients that are derived from wheat, barley, or rye. The comment period closed on March 20, 2012, and FDA's Center for Drug Evaluation and Research is reviewing those comments.[14]

The lack of labeling requirements for gluten in medication impacts the entire spectrum of healthcare participants: prescribers, pharmacists and patients. Complicating regulatory bodies' charge to prevent harm is the lack of qualifiable, peer-reviewed research to demonstrate the harm posed to the end user. The celiac disease and gluten sensitive patient population has long reported reactions to gluten in medication. Beyond this preliminary study, there continues to be a need to demonstrate a cause and effect relationship between gluten in medicine and damage to the intestines in the celiac disease patient population.

Changing Concepts:

Research conducted in 2007 and 2008 indicates that people with celiac disease cannot tolerate as little as 10-50 mg gluten/day.[15] [16] These studies explored the immune response to gluten in people affected with celiac disease as observed through villous atrophy, serology, and reports

of clinical symptoms. Some of the studies did not consider the subjects' symptoms, only histological response. This begs the question: Does a product contain a safe level of gluten if it does not result in an observable (through serology or biopsy) immune mediated response, but does result in untoward effects (symptoms)?

In 2011, the FDA conducted an evaluation of existing research to determine what are tolerable amounts of gluten for people with celiac disease. It found that the tolerable daily intake level of gluten for people with celiac disease was determined to be 0.4 mg gluten/day for adverse morphological effects and 0.015 mg gluten/day for adverse clinical effects.[17]

Preliminary Research:

The area of gluten in medication has received little scientific study. An early (2001) survey of pharmaceutical manufacturers found that respondents warned that their suppliers of raw materials and inactive ingredients could change without notice and that this might affect the gluten status of products.[18] Many drug manufacturers report this same possibility today.

In 2008, NFCA and co-primary investigator Loretta Jay conducted a survey of the celiac disease population who required oral medication when in a Philadelphia area hospital. Seventy-nine percent of respondents reported that neither their physician nor the hospital pharmacist was able to determine if their needed medication contained gluten.

Co-primary investigator Dr. Robert Mangione and his associates conducted an exploratory study in 2010 to evaluate patients' ease of determining if OTC drugs contained gluten by contacting manufacturers. His team found that the time it took to determine the gluten-containing status of medications varied depending on the company. They also found that information manufacturers posted on websites sometimes conflicted with the verbal information they relayed on the phone.[19]

Method:

Through this research study we sought to identify and characterize the problem, qualify the extent of harm, and conduct a root cause analysis. We did this by applying the findings of the patient reported adverse reactions to gluten in medication to existing scientific research: safe threshold of gluten, manifestations of celiac disease, and the ELISA assay.

Since there was little pre-existing research exploring the area of gluten in medicine, we aimed to gain new insights and a better understanding of how the celiac disease and NCGS populations are impacted by unlabeled gluten in medicine with the hope of both awakening the industry and other stakeholders to the potential harm for patients and informing future research.

We first collected data through a survey (see Appendix 1) of the celiac disease and NCGS populations. Those findings were analyzed and a short list of drugs suspected of causing adverse effects was established. Finally, these drugs were tested to determine gluten content, and the findings were compared to the information available to pharmacists, prescribers and patients through both labeling and manufacturer disclosure.

Medications have not been tested for gluten in clinical research prior to this study. The lessons learned here will guide funders, future researchers, manufacturers and regulatory bodies when considering next steps.

Survey:

An online survey instrument was used to distribute, collect and manage the survey results. The majority of questionnaires were distributed electronically. Hard copies of the survey were distributed through medical facilities specializing in celiac disease in order to reach populations that do not have Internet; these were manually entered into the online survey instrument. NFCA and other national celiac disease patient advocacy organizations, academic institutions treating celiac disease patients, and other celiac disease groups and their affiliates were encouraged to host survey-taking opportunities to broaden the survey's reach.

The findings of the survey were analyzed and specific drugs for testing were identified. Criteria for selecting drugs for testing included the number of reported reactions; the severity of the reported reactions; how often the drug is used; and the ability to exclude common drug (non-gluten related) side-effects.

The study population consisted of individuals who voluntarily responded to a request to take the survey. The survey was promoted and distributed to the celiac disease and gluten-sensitive communities through NFCA's distribution lists, the outreach of other celiac disease organizations and groups, and through the media.

Survey inclusion criteria:

- Self-identified individuals following a gluten-free or wheat-free diet
- Males and females
- All ethnicities and races
- Children <18
- Adults ≥18
- Pregnant and/or breastfeeding women

Survey exclusion criteria:

- Individuals who reported that they "Never" or "Occasionally" follow a gluten-free diet were excluded because the investigators were unable to ascertain if the reported reaction was due to the medication or to gluten ingested through the food in the subject's diet.
- Reported adverse events from ingested dietary supplements were excluded from the survey due to their limited regulatory standards and the varied quantity of ingredients.
- Reported adverse events from topical formulations and injections were also excluded as both methods of delivery bypass the gastrointestinal system, and are therefore unlikely to be a cause of gluten-reaction in persons with celiac disease.

Information gathered included demographic characteristics of the respondents, why they are on a gluten-free diet and how they manage that diet. Only subjects who indicated that they always follow a gluten-free diet or usually follow a gluten-free diet had their responses included.

Subjects who reported that they believe that they experienced an adverse drug event due to gluten were asked additional information about the medication, the reaction, and what actions the respondent took as a result of the reaction. Subjects were given the option to share identifying information and to report additional information in narrative form.

Analysis:

- The total number of survey respondents was 5,623
- The total number of respondents who reported they suspected an adverse reaction caused by gluten was 1,399 (25%)
- Survey findings were sorted to meet the criteria of inclusion or exclusion for statistical analysis
- When the incidence of adverse events met inclusion criteria, the name of the medication reported by the respondents was aligned with the corresponding generic name of the active ingredient of the formulation. Doing this allowed the research team to group all brand name and generic drugs together by the medications' generic name.
- Survey respondents named 242 different generic drugs in the survey
- Statistical analyses were performed, including the computation of the frequency of each of the medications (by generic name) reported by the respondents to cause adverse effects
- Only drugs that were named in the survey were considered for testing. Factors that informed the drug selection process:
    - The 10 OTC or Rx drugs most frequently named in the survey
    - National Drug Code (NDC) number provided
    - Dosage and/or manufacturer named by survey respondent
    - Subjects who named a drug suspected of causing an adverse event and who had biopsy diagnosed celiac disease, always followed a gluten-free diet, were not ill and not taking any other medication and had gluten exposure confirmed by a positive biopsy
    - Subjects who reported that they had a biopsy confirmed gluten exposure
    - Top 200 drug products (Rx) prescribed of 2011
    - Common dosage
    - Manufacturer reported product did contain or might contain gluten
    - Gluten-free Drugs, managed by Dr. Steven Plogsted, reported product contains gluten
    - Medications used in disease management for disease with high comorbidity

Selected Medications:

Thirty-nine drugs were selected for testing: 15 OTC drugs and 24 prescription drugs. (See Table 1 on page 11.) Of all the drugs reported (242) by survey respondents, we included the seven most frequently named OTC and eight most frequently named prescription medications for testing. Another 24 drugs were selected for testing; factors that influenced their selection are listed on the previous page. Thirty-three percent (8/24) of the prescription drugs tested were also among the 200 most frequently prescribed drugs of 2011.[20]

Oftentimes survey respondents reported the same generic name drug but identified different manufacturers, dosages or dosage forms. Consequently, we tested more than one formulation

of some drugs that had high frequency. Table 1 lists the drugs by generic name that were selected for testing. If more than one manufacturer or dosage form was tested, the quantity of drug formulations tested is listed in parentheses. We tested both brand name and generic drugs, and we did not test drugs from all manufacturers.

Table 1: Drugs Selected for Testing, Categorized by Generic Name

15 OTC drugs were selected for testing:	24 Rx drugs were selected for testing:
Acetaminophen (2)*	Alprazolam
Acetaminophen/Dextromethophan HBr/Doxylamine succinate	Amoxicillin (2)
Acetylsalicylic Acid	Augmentin (Amox/Clavlanate)
Calcium Carbonate	Azithromycin (2)
Cetirizine	Chlorthalidone
Diphenhydramine HCL	Clindamycin Hydrochloride
Fexofenadine	Desvenlafaxine ER
Ibuprofen (3)	Doxycycline Hyclate
Loratadine (2)	Esomeprazole
Naproxen	Fenofibrate
Pseudoephedrine HCL EXR	Gabapentin
	Levothyroxine (4)
	Lisinopril
	Metformin
	Metoprolol Tartrate
	Omeprazole
	Sertraline
	Simvastatin
	Tramadol

** The number in parentheses represents the quantity of each drug tested, from multiple brands/manufacturers, if greater than one.*

Testing:

Samples of each of the selected drug products were tested using R-Biopharm's testing kits, RIDASCREEN® Gliadin R7001 (a 96 well sandwich ELISA) and RIDASCREEN® Gliadin competitive R7021 (a 96 well competitive ELISA), to determine if gluten was present or absent in the medication's formulations. The tests are intended to assess gliadin/gluten in hot and cold food, and a collaborative study of the Working Group on Prolamin Analysis and Toxicity reported at its September 2012 meeting that it is capable of doing this with sufficient sensitivity and precision.[21] There are no assays in existence specifically meant to test for gluten in medications.

Both the Sandwich and Competitive testing kits were used to detect gluten in variable forms. An epitope is the portion of the gluten molecule that is recognized by the antibody in the assay. A Sandwich format ELISA requires two epitopes to be present in order to elicit a positive test response, while a Competitive format only requires one. When molecules are complete, there are more than enough epitopes present to satisfy the Sandwich format. However, some forms of processing cause hydrolysis of the gluten proteins, which break them down to varying extents. In these cases, the protein may still be complete enough to cause a reaction in a

sensitive person, but may not have the two epitopes needed to show a positive result in the Sandwich ELISA. Since the Competitive format only requires one site, and the specific epitope used to calibrate the assay is very stable, it is able to detect positives in these situations where the Sandwich would fail.

The medications were prepared in the following manner:

- Suspension powder: Water was not used to reconstitute the substance. Because the product was already homogenized, the powder itself was used for sampling.
- Suspension liquid: The suspension was treated as a homogenized sample and it was tested in its dispensed form.
- Tablets: Tablets were crushed with a mortar and pestle, and the needed amount of medication was weighed for testing.
- Liquid capsules (Competitive ELISA): The target mass needed was 1000 mg (1 gram) for Competitive assays. The liquid capsules were added into a test tube and a 60% ethanol solution (prepared in deionized water) was added proportionately by using a 1 g sample/10 ml 60% ethanol ratio (e.g. if the mass of the sample was 1.5 grams, 15 ml of 60% ethanol was added.) The combined capsules and ethanol were heated at 50 degrees Celsius until liquefied. (Although melting occurs at 35 degrees Celsius, the higher temperature was used to expedite the process.) Once liquefied, the sample was shaken for 10 minutes to ensure uniform distribution. Samples were centrifuged and the supernatant was transferred into a secondary test tube. 20 uL of supernatant was aliquoted and diluted with 980 uL of sample diluent, and 50 uL of this solution was used for ELISA testing.
- Solid capsules with granules (Competitive ELISA): The same process was followed as the liquid capsules, but the granules were crushed in the mortar and pestle before being placed in the test tube. The hard shells (capsules) were inserted into the test tube with the crushed granules, 60% ethanol was added as described above, and the mixture was heated to 50 degrees Celsius until liquefied, before being placed on a shaker for 10 minutes. Samples were then centrifuged and the supernatant was transferred into a secondary test tube. 20 uL of supernatant was aliquoted and diluted with 980 uL of sample diluent, and 50 uL of this solution was used for ELISA testing.
- Liquid capsules and solid capsules with granules (Sandwich ELISA): The target mass needed for Sandwich assays was 250 mg. A cocktail, which came with the assay kit, was added to the drug product proportionately to the mass of capsules by a ratio of 250 mg sample /2.5 ml cocktail (e.g. if the mass of the sample was one gram, 10 ml of cocktail was used). The cocktail and drug product were heated together in a test tube at 50 degrees Celsius for 40 minutes. Samples were allowed to cool and then 7.5 mL of an 80% ethanol solution was added. Samples were then placed on a shaker for one hour and thereafter centrifuged for 10 minutes. The supernatant was transferred into a secondary test tube, and 80 uL of supernatant was aliquoted and diluted with 920 uL of sample diluent. 100 uL of this solution was used for ELISA testing.

All identified drugs were analyzed for gluten content using both the Sandwich ELISA and Competitive ELISA assays. The protocols accompanying the testing kits were followed. The samples for analysis included both liquid and solid dosage forms. Both of the assays are commercially available and based on the monoclonal R5 antibody (enzyme-linked immunosorbent assay) that recognizes the QQPFP epitope of gliadin (glutamine-glutamine-proline-phenylalanine); this potentially toxic sequence occurs repeatedly in the prolamin molecules and is where most toxic peptides come from.

We abided by the Codex Alimentarius recommendations. Both the Sandwich assay's gliadin concentration in microgram/kilogram (µg/kg), and the Competitive assay's gliadin concentration in nanogram/milliliter (ng/ml) were read from a calibration curve. To calculate the gluten concentration for the assays, these concentrations were multiplied by the dilution factor of 500, and the results were multiplied by a factor of two. All assays were conducted in duplicate.

Results:

Thirty-nine drugs were tested for gluten: 24 prescription drugs and 15 OTC drugs. All tests were completed in duplicate, and some drugs were tested a second time (also in duplicate). The assays measured the concentration of gluten in the drug products. Some drugs did test over the level of quantification (LOQ) for the Competitive ELISA, but none of the medications tested over the LOQ for the Sandwich ELISA.

When drug products tested over the LOQ we had confidence in the test findings. Some other drug products tested at a level of detection (LOD), but below the LOQ. This means that gluten was detected in the drug product, but we had little confidence in the quantity that was there.

Although less than 20 ppm is the standard used to determine if a food product contains gluten,[22] no such qualification has been made for medication. Therefore, we opted to report on the actual test findings: both ppm, and mg/dosage form.

The calculated gluten concentrations from each analysis were multiplied by the dilution factor specified in the manufacturer's protocol, and the result was used to calculate the concentration of gluten (in ppm) per dosage form.

When researching medications we referenced Daily Med, a website managed by the National Library of Medicine (NLM) as a public service. It is a resource about marketed drugs commonly available to healthcare providers and the general public. Package inserts that accompany medications and known side effects of medicines are among the types of information included on this website. It can be accessed at http://dailymed.nlm.nih.gov/.

When embarking on this study, we carefully considered what we could ascertain from the research design. The goal was not to quantify any gluten found in medications. Rather, we sought to better understand the experiences people with celiac disease had with gluten in medicine, and identify causes of adverse drug events. To keep the focus on these primary questions, information that identifies the manufacturer of the medication (e.g. the specific brand names of the drugs,) or its test results has been omitted from this report. This is consistent with the title of the study, "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."

Competitive ELISA

The Competitive ELISA is performed to test for gluten in hydrolyzed products. The Competitive ELISA's LOQ is 10 parts per million (ppm). Testing that results in an amount above the LOQ is considered "positive."

Three drugs could not be tested by the Competitive ELISA method because the emulsion process left some of the samples in solid form; they would not break-up and we were left without liquid sample to analyze. The drugs were: loratadine 10 mg capsules; desvenlafaxine ER 100 mg tablets; and pseudoephedrine HCL 120 mg caplets.

Three drugs tested above the LOQ on the Competitive ELISA.

1. Sertraline HCl film coated 50 mg tablets were tested two times, each in duplicate. In order to reach the required 1000 mg for the competitive testing, 6.53 tablets were prepared. After the testing was completed, the concentration was calculated to be 77.13 ppm during the first testing, and 54.46 ppm during the second testing.

   Daily Med reports that each tablet contains **sodium starch glycolate** (red flag ingredient, source not specified) in addition to other ingredients. No hydrolyzed products appear to be listed as ingredients.

   The manufacturer made a definitive statement during a phone call that its sertraline tablets do not contain any gluten-containing ingredients; the manufacturer bases this on a written questionnaire that they send to the makers of the source ingredients. They reported the source of the sodium starch glycolate to be potato and corn. A follow-up inquiry revealed that the makers of the source ingredients do not complete the survey each time a batch of product is delivered. The manufacturer further stated that the ingredient suppliers are not required to disclose if the product is changed to an equivalent product, as long as a United States Pharmacopeia (USP) grade product is supplied.

   Sertraline was the 5th most reported drug in our survey, with 12 people suspecting it as the source of gluten exposure. One person provided the same NDC number as the drug that was tested.

2. Acetaminophen/dextromethophan HBr/doxylamine liquid capsules tested above the LOQ as well. Unlike sertraline, which required more than six tablets, only 0.64 of a dosage form (liquid capsule) was needed to fulfill the required 1000 mg for the competitive testing. It tested at 22.4 ppm.

   Daily Med doesn't list any red flag ingredients in the acetaminophen/dextromethophan HBr/doxylamine that we tested. When we called the manufacturer to ask if the product contained gluten, the customer service representative said that while some of their products are tested for gluten, this product has not been tested. They "do not label or claim that the product is gluten-free."

   Seven survey respondents indicated that they believed acetaminophen/dextromethophan HBr/doxylamine succinate was a source of gluten exposure. This ranked the drug as the 8th most frequently reported OTC drug in our survey.

3. Omeprazole 40 mg capsules were tested two times, and both times in duplicate; the results were 22.56 ppm and 25.26 ppm respectively. Unfortunately, the number of capsules that was used to create the testing product was not documented.

None of the inactive ingredients listed in Daily Med for the omeprazole 40 mg capsules that we tested is a red-flag ingredient that may be sourced from gluten. A pharmacist from the manufacturer reported that, based on the ingredients, their omeprazole capsules don't contain gluten, but she offered a disclaimer that since the final product is not tested, they cannot certify this. When asked, the pharmacist said that there is a chance of cross-contamination (cross-contact) with another product.

Omeprazole is available in both OTC (20mg) and prescription (40mg) formulations, and both doses were reported by nine survey respondents to be the source of a suspected gluten-reaction. Of the survey respondents who provided a dosage, three listed 40mg and two listed 20 mg.

Omeprazole belongs to a class of drugs called proton pump inhibitors (PPIs), which decrease the amount of acid produced in the stomach. Daily Med lists the most common side effects of omeprazole to be headache, stomach pain, nausea, diarrhea, vomiting and gas. Children between the ages of 2 – 16 years also report respiratory system events and fever.

Gastrointestinal complaints are the most common side effects of omeprazole, and also a common manifestation of celiac disease and NCGS. We selected this drug as an example to compare the known side effects of omeprazole with the suspected adverse reactions reported by the survey respondents.

The survey respondents named ten different suspected adverse reactions from omeprazole, four of which impacted the gastrointestinal tract; constipation (2) was named two times, nausea (5) and diarrhea (5) were both named five times, and abdominal pain or bloating (9) was named nine times. Other adverse reactions reported by survey respondents include headache (1), **fatigue (1), Irritability (3), muscle tremors/cramps (2), failure to thrive (1), skin rash (2).** The reactions reported by survey respondents that are not known side effects of omeprazole are listed in bold. The number in parentheses is how many people listed that complaint in the survey.

Sandwich ELISA:

The Sandwich ELISA's Limits of Quantification (LOQ) is 5 parts per million (ppm). No drugs tested positive using the Sandwich ELISA, as none of the drugs tested above the LOQ (5 ppm).

Discussion:

When analyzing survey and testing results we strived to support the goal of *maximizing the benefits and minimizing the risk* to the celiac disease and NCGS populations. By characterizing the factors that lead to adverse drug events, and the elements that are needed to identify risk, we established a foundation of knowledge to be built upon. Our hope is that action will be taken so individuals following a medically required gluten-free diet will have access to the full spectrum of available medications and also can avoid preventable harm.

Labeling:

As previously stated, there are no guidelines or regulations to advise drug manufacturers about how to label the inactive ingredients in medications that may contain gluten. Consequently, manufacturers and packaging companies are faced with predicaments such as:

- What language should they use to accurately describe the source of excipients in their drug products?
- How much information should be provided?
- Should they test the final product? Should they assert that their drug is gluten-free, or just let the end user or pharmacist figure it out with the information that is provided?
- What should manufacturers do to meet the needs of the community while still meeting the company's legal needs?

We examined an OTC antacid/calcium supplement tablet of one particular manufacturer as an example of a labeling challenge. Seven survey subjects named calcium carbonate as the cause of their suspected adverse drug event. Although Daily Med lists a starch among the inactive ingredients for this particular product, the source is identified; no red-flag ingredients are listed in the ingredients of this product.

The Daily Med product information packaging (principal display panel) states that the product is "gluten-free," but the manufacturer reports on its website's FAQ section conflicting and confusing information. Specifically, the website's FAQ states that gluten is not used as filler, but that there may be trace amounts from ingredients supplied by outside vendors. The website continues to explain that the consumer should review the inactive ingredients.

Although a medication may have no gluten in it, this study demonstrated that a label's lack of clarity regarding the source of ingredients or other communication about ingredients provided by the manufacturer could create an adverse event. For example, a patient may not adhere to a prescribed regimen, or the patient's therapy may be changed to a second line regimen because of unknown or suspected information. Based on the definition cited earlier in this report, this constitutes an adverse drug event. Specifically labeling the gluten content of prescription and OTC drugs could prevent these adverse events from occurring.

Red-Flag Ingredients:

As listed in the Pharmacists Dilemma section on page 6, 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. Significantly, none of the manufacturers of drugs named in the survey that we contacted gave a definitive statement to our investigative team that their product contained gluten.

Since we strove to identify any and all gluten that might be in the drug products, all the drugs were tested with both the Competitive ELISA and the Sandwich ELISA. Because the two assays measure different compositions of gluten, a drug product can (and did) test positive on one assay and not the other. Gluten that has been hydrolyzed has been broken down into its component amino acids; the Competitive ELISA tests for this. Gluten that remains in its original form is measured with the Sandwich ELISA.

Most of the drugs that tested above the LOQ in the Competitive ELISA did not contain any red-flag ingredients. In addition, there were positive test results for the Competitive ELISA, which tests for gluten in hydrolyzed products, and there were no hydrolyzed products among the ingredients listed by the manufacturer.

Reasons for these test results might include:

- Manufacturer's cross-contamination (cross-contact)
- Manufacturer's outdated information about ingredient's source
- Contamination in the lab
- A false-positive with the assay

Testing Methods:

Throughout the analysis and reporting process, we considered how the patient and prescriber populations would use our findings. We concluded that it is important to report the quantification of gluten per dosage form, rather than in their raw, or testing form.

Four drugs (esomeprazole capsules, tramadol tablets, diphenhydramine HCL tablets and chlorthalidone tablets) tested positive in the Competitive ELISA when their gluten concentrations were examined (ppm) in raw form. But, when the results were corrected to determine the gluten concentration (ppm) per tablet/capsule, the results for all of these medications fell below 10 ppm, the level of quantification. For this reason, we are reporting that these drugs tested below the LOQ, and therefore negative for gluten.

The interpretation of 15 Sandwich ELISA tests presented some challenges. The samples for each drug quantitated below the analytical LOQ of 5ppm. Because the extraction protocol used for the Sandwich ELISA requires that only 250 mg of drug be extracted for the Sandwich analysis, less than one oral dosage form was used in these cases. When we corrected the numbers to determine a "concentration per tablet," the calculated gluten concentration of each drug product was multiplied and resulted above the LOQ. We believe that these results lack validity. Any quantitative values below the LOQ of the assay are unreliable, and cannot be extrapolated to accurately label a sample as positive.

The research team experienced this particular problem with only one drug tested using the Competitive ELISA; One gram of drug needs to be extracted for this testing process, so there was a larger sample to draw from.

The following is an example of the results of the Sandwich analysis of the calcium carbonate sample that was tested:

> The calculated concentration based on the ELISA is 2.88 ppm. This is below the analytical LOQ and therefore cannot be reliably and accurately quantitated. In the preparation of this sample, 0.13 tablets were used for extraction (0.13 tablets weighed 250 mg.) When applying the correction factor for gluten concentration per 1.0 tablet, 2.88 ppm would have to be multiplied and the resulting concentration becomes 22.15 ppm (over the LOQ).

From an analytical standpoint, we are lacking a sound basis to take an unreliable quantitative value below the LOQ and multiply it to obtain a concentration that could be labeled as significant.

We are including these findings here as they lead to additional questions:

- What is the best way to test drugs? How is testing drugs different from testing food?
- Is there a testing method in existence for application to drug samples (that uses much smaller quantities compared to food) that would be a better fit?

A review of the literature reveals that there are numerous articles describing the use of various assay methods to test for gluten in foods. Unfortunately, the use of assays to evaluate for the presence of gluten in drugs has not received such attention. Moving forward, including the manufacturers of assays in stakeholder discussions is necessary.

Data Analysis:

The FDA team analyzed the data from our testing using a data analysis computer program that was supplied by R Biopharm, the maker of the testing kit. Our team did not have access to the computer analysis program during the testing and analysis period, and instead analyzed the data manually. Although the computerized analysis is more exact, the manual analysis proved to be accurate. One drug, amoxicillin, had a slight variation between the two methods, as described below.

Amoxicillin suspension 250 mg/5 ml was tested and the quantitative value for gluten was determined to be positive, though just above the LOQ (before correcting the result to reflect a per tablet amount) using a linear calibration curve. The FDA processed the same data using a cubic spline curve. Using this method, the FDA determined the concentration of the amoxicillin suspension to be just below 10 ppm and negative. Given this discrepancy in testing results near the assay LOQ and the FDA's use of advanced regression software, our team made the determination to report this drug as below the LOQ and negative.

Amoxicillin was the third most reported prescription drug in the survey, with 16 subjects naming it as the source of their suspected gluten exposure.

Cause and Effect:

When we proposed this project, we knew that the study design would not allow us to show a cause and effect relationship between potential gluten in a medication and a survey respondent's reported adverse events that they attribute to gluten. Rather, we expected to demonstrate that because the gluten content of medicine was unknown, the celiac disease and NCGS patient populations would attribute any adverse drug events to gluten, even if caused by the drug itself.

People with celiac disease and NCGS experience more than 300 different clinical reactions to ingesting gluten. Manifestations may involve the neurological, gastrointestinal, cardiovascular, muscular, skeletal, dental, skin, mucosal and reproductive systems. Many, if not most, of these reactions are also common side effects of various medications.

Levothyroxine sodium tablets were the most common prescription drug reported in the survey: 49 subjects reported that they suspected gluten in levothyroxine caused their adverse drug events. The medication is used to treat hypothyroidism, a condition that has a high co-morbidity with celiac disease. Several brand and generic manufacturers of levothyroxine are available. The patient medication insert that accompanies a frequently prescribed levothyroxine sodium tablet states that there are no known adverse reactions to the levothyroxine therapy, but primarily those of hyperthyroidism due to therapeutic over-dosage."[23] All of the manifestations reported by those who said they thought gluten in the levothyroxine sodium tablets was the cause of their gluten exposure are also listed as possible side effects from hyperthyroidism (or too much levothyroxine.)

An interesting observation is that many survey respondents reported that when they switched from one brand to another brand/manufacturer of the same drug that the symptoms experienced went away. This would lead one to believe that it is not the active ingredient in the medication that caused the symptoms, but rather the inactive ingredients.

Emotional Harm:

This study does show the celiac disease and NCGS populations experienced what *they believe* to be gluten exposure from medication. Virtually all respondents said that when they stopped taking the medication their symptoms went away. While this relationship will be consistent with the active ingredient of the drug product causing the side effect, it also confirms the consumers' *perception* that gluten in inactive ingredients of the medication caused the reaction.

Patients experienced anxiety and they did not adhere to prescribed medication regimens. This was not an isolated case of patients going it alone. Sometimes ending a treatment regimen was against medical advice (AMA), but 37% of respondents reported that their healthcare provider either stopped the medication or changed to a different brand or drug. We do not know from the survey responses if the healthcare provider's decision to change the medication was due to the provider's suspicion that gluten caused the adverse effect, or if the provider suspected it was a side effect of the active ingredient in the drug.

Once the patient perceives that an adverse event is caused by gluten in the medication, it becomes more challenging to convince them of another cause. Some comments made by individuals who took the survey include:

- 7111407: (…The manufacturer) has since written a disclaimer stating that it has never ever had any gluten in it. Oh, yes it did so.
- 7237272: My celiac disease is not healed … I could not find any other source of gluten in my diet so changed the medication because the company did not check for gluten contamination.
- 7340014: The doctor told me to keep taking the medicine. Needless to say, I didn't take it or see him again.

When an individual or healthcare provider is unsure of the gluten status of a medicine, or loses confidence in the drug manufacturer's ability to deliver a gluten-free medication, then additional harm may occur. The first choice medication may not be prescribed and this may prolong the illness that is being treated. If patients lack trust with the prescribed drug then there are adherence concerns as well.

Financial Cost:

As a result of incomplete information, patients are experiencing unnecessary referrals to other medical specialists, unnecessary medical procedures, and missed time from work. This results in avoidable healthcare costs and loss of income.

- 24% of respondents who reported adverse events said that they stayed home from work or school as a result of the symptoms experienced
- 22% of respondents who reported adverse events said that their healthcare provider prescribed a medication to treat the symptoms experienced
- 5% of respondents who reported adverse events said that either blood work to measure gluten antibodies or an upper endoscopy (esophagogastroduodenoscopy or EGD) to assess small intestinal damage was performed

Some patients are taking matters into their own hands due to the lack of confidence in the response from the healthcare system. In other cases, the healthcare provider is pursuing a cause.

- 7075987: Had to go to hospital to get help (as) doctor did nothing – said medication couldn't cause problems since (its) safe.
- 7286564: Sent to ER. Abdominal/pelvic ultrasound did not show anything.
- 7110532: (Physician) referred me to proctologist. Colonoscopy negative.
- 7135330: Doctor did a spinal tap on (child) because of her symptoms. We knew it was gluten, but they still did it to make sure.

Clinical Significance:

The Office of Food Safety at the FDA concluded in its May 2011 Health Hazard Assessment for Gluten Exposure in Individuals with Celiac Disease that those affected with the disorder should consume no more than 0.4mg gluten per day to prevent adverse morphological effects and 0.015 mg gluten per day to prevent adverse clinical effects.[24]

In addition to testing above the LOQ, the three drugs that tested positive using the Competitive assay contained gluten at a level above 0.015 mg per dosage form:

- Sertraline tablets were tested two times. When the amount of gluten per dosage form was calculated, we determined that there was 0.077 mg gluten during the first test, and 0.054 mg gluten in the second test.
- Acetaminophen/dextromethorphan HBr/doxylamine liquid capsules were tested one time and they contained 0.022 mg gluten per dosage form.
- Omeprazole capsules were tested two times. The first time they contained 0.023 mg gluten per dosage form. The second time they were tested they contained 0.025 mg gluten per dosage form.

When we calculated the gluten content of all of the drugs, several of the drugs tested (using the Competitive assay, which tests for hydrolyzed gluten) contained gluten in quantities that would result in adverse clinical effects if two or more dosage forms were given in one day. The initial test results were at a level of detection but below 10 ppm gluten, which is below the LOQ. As a result, the calculation to determine milligrams gluten per dosage form is based on less-than-reliable data and may not be accurate. Despite this, we included this information for

discussion purposes only, as the levels of gluten meet the threshold previously determined to cause adverse clinical effects.

Survey Limitations:

The survey did not reach a representative sampling of the celiac disease and NCGS patient populations, nor were respondents randomized.

The survey was electronically distributed to the celiac disease and NCGS populations through various channels: NFCA and other celiac disease organizations included the survey in their outreach efforts; it was promoted on celiac disease listservs; it received blogger and media coverage; and some medical facilities specializing in celiac disease distributed the survey to their patients. Despite efforts to reach populations without access to a computer or the Internet, less than one percent of the completed surveys were non-electronic.

Since the total number of individuals who received the survey is unknown, we are unable to determine its response rate. Furthermore, by virtue of their connection to celiac disease organizations or media sources, it is likely that the population that did receive the survey is more attentive to the gluten-free aspects of their lifestyle than the general celiac disease and NCGS populations.

Another limitation is the reliability of the finding that 25% of survey respondents suspected an adverse reaction was caused by gluten in medicine. Since the topic of the survey was known, it is probable that individuals who believed they had experienced an adverse drug event would be more likely to take the time to complete the survey than the general celiac disease and NCGS populations; they had a personal interest in the subject matter. Therefore, we *cannot* generalize this result by applying the 25% finding to the entire population with celiac disease or NCGS.

Testing Limitations:

Many survey subjects provided NDC and lot numbers of drugs that they suspected gave them adverse effects. Ideally, we would have preferred to test drugs that were from the same batch of medicine as was reported to have caused a suspected adverse reaction. Although we did test some drugs with the same NDC number reported, we could not locate any medications that had the same lot number. This was disappointing but expected, as the drug life cycle between manufacture and distribution can be lengthy, and survey subjects were permitted to recall events that took place in the past.

Conclusion:

The findings of this study about gluten in medicine extend significantly beyond the question, “Is there gluten in that drug?” There are many facets for stakeholders to consider. Collaboration between the FDA, drug manufacturers, manufacturers of testing kits, healthcare providers and the celiac disease and NCGS community is needed.

People following a medically required gluten-free diet have long held apprehension and anxiety about the food and medicine they ingest. Many harbor distrust of the healthcare system because their road to a diagnosis was long and well traveled. When manufacturers use clear,

unambiguous language about the inactive ingredients in their products, the end users and their healthcare professionals will have greater trust in the message and the product.

The qualified findings of the survey, coupled with the test results of the identified medications, provide the preliminary basis for further study in this area. We recommend pursuing the development of optimum testing protocols, and determining if there is clinical significance to the identified amounts of gluten that is present in medicine.

In addition, we recommend that to prevent further avoidable adverse drug events, guidance should be given to drug manufacturers on appropriate labeling of inactive ingredients. It is expected that by providing prescribers, pharmacists and patients with needed information to make informed decisions, the incidence of adverse drug events can be reduced. As a result, this may have an impact on prescriber and patient medication decision making, which will also impact the marketplace.

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Appendix 1

Welcome!

The National Foundation for Celiac Awareness (NFCA) is working with St. John's University College of Pharmacy and Allied Health Professions to study the effect on people who follow a gluten-free diet if they take medicine that contains gluten, a protein in wheat, barley and rye. The US Food and Drug Administration is funding this research study.

The study has two parts. First we will conduct this survey, and then we will test some medicines to see if they contain gluten. The results of this survey will help us learn more about people's experiences, and will help us decide which medicines we will test for gluten. Together these findings could help the medical and scientific communities see that more research and investigation are needed.

People who are following a gluten-free or a wheat-free diet may take this survey, or may have someone take the survey for them. By taking this survey, you are giving permission for you or the subject of the survey to be involved in this research study.

This survey will take between 4 and 15 minutes to complete, depending on your responses.

Please return completed survey to NFCA, PO Box 544, Ambler, PA 19002

Survey: Gluten in Medication

1. Please indicate if you are taking this survey for
    a. Yourself
    b. Your child
    c. Other (specify) _____

Please answer all questions for the person who is the subject of the survey, as reported in question #1. For example, if you are answering questions for yourself, then you are the subject. Respond about you. If you are answering questions for your child as the subject, then all answers should be about your child.

2. Why are you following a gluten-free or wheat-free diet? Please circle all that apply.
    a. Celiac disease
        i. Diagnosed by biopsy
        ii. Diagnosed by serology (blood test)
    b. Non-celiac gluten-sensitive/intolerance
        i. Diagnosed by healthcare provider
        ii. Self-diagnosed
        iii. Diagnosed by stool sample
    c. Dermatitis Herpetiformis (DH)
        i. Diagnosed by biopsy
        ii. Self-diagnosed
    d. Wheat allergy
    e. I feel better when on a gluten-free diet even though I have not been diagnosed with celiac disease, dermatitis herpetiformis, a gluten sensitivity or a wheat allergy
    f. None of the above
3. Please indicate how long you have been following a gluten-free diet.
    a. Less than one year
    b. 1-2 years
    c. 3-5 years
    d. 6-9 years
    e. 10 or more years

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4. How regularly do you follow a gluten-free diet? Please circle the *one* best answer for the subject of the survey.
    a. Always: Check ingredients and avoid cross contamination at home and when away from home
    b. Usually: Take some risks when away from home
    c. Occasionally: Stay gluten-free when it is convenient (Go to question #24)
    d. Never: Frequently eat food that contains gluten (Go to question #24)
5. How often do you or your healthcare providers (doctors, nurses, pharmacists, etc.) check for gluten in the ingredients of prescription or over-the-counter (OTC) medicine? Please circle the *one* best answer for the subject of the survey.
    a. Always: Check ingredients for gluten routinely when taking medicine
    b. Usually Check ingredients for gluten most of the time
    c. Occasionally: Check ingredients for gluten once in a while
    d. Never (Go to question #7)
6. How do you check if a medicine contains gluten? Please circle all that apply.
    a. Call or email manufacturer or visit manufacturer's website
    b. Read the label or product insert
    c. Check www.glutenfreedrugs.com or other independent website or list
    d. Ask my pharmacist
    e. Ask the person who prescribed the medicine
    f. Other (specify)

    _____
    _____
    _____
7. Have you ever had a reaction to a medicine that you think might have been caused by gluten?
    a. Yes
    b. No (Go to question #24.)

Please answer the following questions for the medicine that you think caused a gluten exposure reaction. Please answer all questions about the same medicine.

8. Was it a dietary supplement? Dietary supplements include vitamins, herbal treatments, minerals, amino acids, etc.)
    a. Yes (Go to question #24)
    b. No
    c. Don't know

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9. Was it a generic medicine?
    a. Yes
    b. No
    c. Don't know
10. What form was the medicine in?
    a. Oral suspension (liquid)
    b. Pill
        i. Tablet
        ii. Caplet
        iii. Capsule
        iv. Don't know
    c. Sprinkle
    d. Oral disintegrating tablet (ODT) or lozenge
    e. Eye drop/ear drop/nasal spray or drop
    f. Ointment/cream/foam
    g. Inhaled
    h. Don't know
    i. Other (Specify) _____
11. Please provide whatever information you know about the medicine.
    a. Name of the medicine _____
    b. Dosage _____
    c. Manufacturer _____
    d. National Drug Code number (NDC#) _____
    e. Lot number _____
    f. Store purchased _____
    g. City/State purchased _____
    h. Other _____

    _____
12. What year did this experience occur? _____

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13. Did you try to check the ingredients of this medicine before taking it? Please circle all that apply.
    a. No, I didn't try to check the ingredients before taking the medicine (Go to question #15)
    b. I called or emailed the manufacturer or visited manufacturer's website
    c. I read the label or product insert
    d. I checked www.glutenfreedrugs.com or other independent website or list
    e. I contacted a celiac support organization to ask for advice
    f. I asked my pharmacist
    g. I asked the person who prescribed the medicine
    h. Other (Specify) _____
    _____

14. Did you have any problems when trying to check if there was gluten in the medicine? Please circle all that apply.
    a. No problems
    b. My pharmacist did not know if the medicine had gluten in it
    c. The person who prescribed the medicine did not know if the medicine had gluten in it
    d. The manufacturer needed time to research the ingredients
    e. No one from the manufacturer answered my email or phone call
    f. I couldn't find the information on the manufacturer's website
    g. I couldn't understand the label or product insert
    h. The independent websites or lists that I checked didn't have the medicine listed
    i. Other (Specify) _____
    _____

15. Please describe the reaction that you had. Please circle all that apply.
    a. Nausea
    b. Vomiting
    c. Diarrhea
    d. Constipation
    e. Abdominal pain or bloating/gas
    f. Headache
    g. Depression/anxiety
    h. Seizures
    i. Fatigue
    j. Irritability
    k. Muscle tremors or cramps
    l. Arthritis
    m. Anemia
    n. Hot flashes or night sweats
    o. Failure to thrive
    p. Skin rash
    q. Canker sores or mouth sores
    r. Hair loss
    s. Other (Specify) _____
    _____

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16. How much time passed from when you started taking the medicine and the reaction you think was caused by the medicine?
    a. Immediate/less than one hour
    b. Within 24 hours
    c. Within 3 days
    d. Within 7 days
    e. Within 14 days
    f. Within 30 days
    g. Don't know
17. How long did you take the medicine before you thought it was what caused your reaction?
    a. 24 hours
    b. 3 days
    c. 7 days
    d. 30 days
    e. 1-3 months
    f. 4-6 months
    g. More than 6 months
    h. Don't know
18. What made you think it was the medicine that caused the reaction? Please circle all that apply.
    a. I looked into the ingredients of this medicine and discovered it MIGHT have gluten in it
    b. I looked into the ingredients of this medicine and discovered it DID have gluten in it
    c. I looked into the ingredients of other medicines and dietary supplements in my diet and learned they did NOT have gluten
    d. I looked into the ingredients of foods in my diet and learned that they did NOT have gluten
    e. I stopped taking the medicine and the reaction went away
    f. Blood test: positive serology for gluten exposure
    g. Endoscopy: positive biopsy for gluten exposure
    h. Home gluten-testing kit: medicine was tested. Please explain _____
    _____
    i. Other (Specify) _____
    _____
19. Did you contact the manufacturer regarding the reaction?
    a. Yes
    b. No (Go to question #21)
20. What was the manufacturer's response? Please circle all that apply.
    a. They wrote down the complaint
    b. They said there WAS gluten in the medicine
    c. They said that there MIGHT BE gluten in the medicine
    d. They said that there was NO gluten in the medicine
    e. They said that they DO NOT ADD gluten to the product, but cannot say that it is gluten-free.
    f. They said they would research the medicine and get back to me
    g. Other (Specify) _____
    _____

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21. What did you do in response to the symptoms of your reaction? Please circle all that apply.
    a. Nothing
    b. I contacted my doctor or primary healthcare provider. In response to the situation my healthcare provider
        i. Prescribed medicine
        ii. Performed an upper endoscopy (EGD) or colonoscopy
        iii. Ordered blood work/serology
        iv. Did nothing
        v. Other (Specify) _____
    c. I contacted my pharmacist
    d. I took over-the-counter (non-prescription) medicine
    e. I rested / stayed home from work or school
    f. Other (Specify): _____
    _____
    _____

22. Were you taking any other medicines or dietary supplements at the time of the reaction? Please circle all that apply.
    a. No
    b. Don't know
    c. Multivitamins
    d. Thyroid medicine
    e. Diabetes medicine
    f. Psychiatric medicine
    g. Heart medicine
    h. Cholesterol medicine
    i. Asthma medicine
    j. Other (Specify) _____

23. Did you have a cold, the flu or a virus at the time of the reaction?
    a. Yes
    b. No
    c. Don't know

24. What is the age of the survey subject? _____

25. What is the gender of the subject of this survey?
    a. Male
    b. Female

26. How does the subject of the survey identify him/herself?
    a. American Indian/Native American
    b. Asian
    c. Black/African American
    d. Hispanic/Latino
    e. White/Caucasian
    f. Pacific Islander
    g. Other (Specify) _____

Please return completed survey to NFCA, PO Box 544, Ambler, PA 19002

27. What is the highest level of education completed by either you or the adult responsible for the subject of the survey?
    a. Less than high school
    b. High school/GED
    c. Some college
    d. 2 year college degree (Associates degree)
    e. 4 year college degree(BS/BA)
    f. Advanced degree (Masters/Doctorate/Professional)

28. Sometimes additional information is needed about the medicine involved or a person's reaction. May we contact you for additional information if needed? (Optional)

    a. Email _____
    b. Name _____
    c. Address _____
    d. Town/City _____
    e. State _____
    f. Zip Code _____
    g. Phone _____

29. If you like, you may share additional information here.

_____

_____

_____

_____

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Thank you!

Thank you very much for taking the time to share your experiences. Your input helps the National Foundation for Celiac Awareness (NFCA) continue our work to improve the quality of life of people with celiac disease and gluten sensitivity.

We are pleased and proud to partner with co-Primary Investigator Dr. Robert Mangione, Dean and Professor of St. John's University College of Pharmacy and Allied Health Professions and his team. We also acknowledge and are grateful for the support of the US Food and Drug Administration's Safe Use Initiative. Additional information about the Safe Use Initiative can be found at www.fda.gov/safeuseinitiative.

You may check on the progress of this research by visiting NFCA's website, www.CeliacCentral.org, where NFCA will post the current status of the research study. The earliest that the final report will be published is 2013. You may request to be notified when the final study report has been published by registering with NFCA at http://www.celiaccentral.org/Gluten-in-Medications-Survey/Thank-You/. Questions and comments regarding this survey can be directed to Loretta Jay, co-Primary Investigator and Consultant to NFCA, at 203.255.7703 or lorettajay@parasolservices.com.

You may keep this last page for future reference.

Please return completed survey to NFCA, PO Box 544, Ambler, PA 19002