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Food and Drug Administration
Dockets Management Branch
Room 1-23
12420 Parklawn Drive
Rockville, MD 20857
(301) 827-6860

Citizen Petition
submitted by Michael Weber of New York State

The undersigned submits in quadruplicate this petition under the Federal Food, Drug, and Cosmetic Act to request the Commissioner of Food and Drugs exclude the use of Wheat Gluten as an excipient in both prescription and OTC drugs under these regulations; 21 CFR 210.3(b)(8), 21CFR 330.1(2)(e)and 184.1322(d).

The following are the regulations, worded exactly

21CFR 210.3(b)(8)
Inactive ingredient means any component other than an *active ingredient.*

21CFR330.1 (2)(e)
The product contains only suitable inactive ingredients which are safe in the amounts administered and do not interfere with the effectiveness of the preparation or with suitable tests or assays to determine if the product meets its professed standards of identity, strength, quality, and purity. Color additives may be used only in accordance with section 721 of the act and subchapter A of this chapter.

184.1322(d) Prior sanctions for this ingredient different from the uses established in this section do not exist or have been waived.

FDA. 2008. P. 0333

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The following is a full statement arguing for the proposed change

The petitioner requests that wheat gluten no longer be considered a safe inactive ingredient for uses as an excipient in medicine regulated by the FDA. If the FDA wishes to continue to recognize wheat gluten as safe, then labeling rules for medications should be brought into conformity with rules now being released for food. This request is based on the biological effects gluten has on individuals who suffer from a medical condition called Celiac Disease.

Individuals with Celiac disease must avoid all consumption of wheat gluten in order to lead healthy lives unaffected by the specific biological reaction they have to Gluten. Currently, Gluten is an accepted excipient, and is considered to be a safe and inactive ingredient. As such, it has no therapeutic effect and is generally recognized as safe (GRAS). However, for a significant subset of the population, approximately 1%, gluten is toxic. This proportion of the population dwarfs those who are affected by phenyketonuria(PKU). The approximately one in 10,000 people with PKU are protected by warning labels on both food and medicines. People with Celiac disease suffer various biological reactions to gluten when it is ingested, even in small amounts. Because gluten can be used as an excipient in a variety of preparations, an individual risks being exposed to it no matter what medication they take, without respect to risk or benefit from the active ingredient of a particular medication. **Since 21CFR330.1 (2)(e) states that "only suitable inactive ingredients which are safe in the amounts administered" may be used as excipients, FDA should recognize the toxicity of gluten for a significant proportion of the population and therefore revoke gluten's GRAS status.**

As more medications move to generic manufacture and the sourcing of both excipients and active ingredients becomes more globalized, it gets harder for pharmacists and consumers to know if

their medications are free of gluten. According to one national pharmacy corporation, CVS, they do not track the gluten content of medicine they dispense. CVS adds that cross contamination of medications at the point of manufacture combined with generic manufacturers' practice of changing preparations without notice, makes it highly unlikely that a patient could be confident their medication is free of Gluten.[1] By the logic of CVS, patients needing to avoid gluten, would need their physician to determine whether the exact prescribed drug is gluten free, and that if the physician has not specified a name brand drug, DAW, then another step must be taken to contact the patient's pharmacy, finding out who made the generic drug at the pharmacy store: But then the manufacturer would have to be contacted, and their practices investigated to an extensive degree. I believe this is a significant burden, both for medical and economic reasons.

An FDA ruling to end gluten's GRAS status would solve this matter at a stroke. Pharmaceutical manufacturers have a variety of excipients at their disposal, such as these listed by IPEC-Americas, an excipient trade group:[2]

> **Magnesium Stearate,Lactose, Microcrystalline Cellulose, Starch (corn), Silicon Dioxide Titanium Dioxide, Stearic Acid, Sodium Starch Glycolate, Gelatin, Talc, Sucrose Calcium Stearate , Povidone , Pregelatinized Starch , Hydroxy Propyl Methylcellulose OPA products (coatings & inks) , Croscarmellose, Hydroxy Propyl Cellulose, Ethylcellulose, Calcium Phosphate (dibasic), Crospovidone, Shellac (and Glaze)**

But exceptions to this petition's proposal should recognize instances where wheat gluten is the necessary excipient in a drug: A label or insert warning would be needed here, to warn pharmacists and Celiacs. As an example, Teva Inc. has stated that in formulations such as flavoring agents for children's medicines, wheat must be used.[3]

The FDA should take into consideration the significant difference in costs between name brand and generic drugs. Patients with Celiac disease would be significantly burdened if they were limited to purchasing name brand drugs because generic drugs were not reliably free of gluten. From one manufacturer to another, and from one production batch to the next, a medication may or may not be made with gluten as an excipient and it is necessary to know the batch number of one's own drug at the time of use in order to have confidence that the preparation is free of gluten.[4] In a paper titled

"The Economic Burden of a Gluten Free Diet," by Anne R. Lee et al, dietician at the Columbia University Celiac Center, it was shown that celiacs already face a heavy cost burden finding suitable foods, free from gluten. Lee wrote, "...it was determined that overall gluten-free products are far more expensive than their regular gluten containing products, at a rate of 2–3 times." If drugs, including generics and OTC, were reliably free of gluten celiac would not continue to face compounded cost burdens.[5] The FDA has already recognized the important health issues surrounding wheat gluten in foods.[6]

Therefore, I petition the FDA to revoke gluten's GRAS classification and remove it from the list of acceptable excipients so that it will no longer be present in prescribed name brand, generic and OTC medications. An exception should be made for drugs where gluten is the only suitable excipient.

Celiac Disease is thought to be a heritable condition affecting about 1% of the United States population.[7] People with Celiac experience a range of symptoms stemming from the consumption of the food protein gluten. Gluten is naturally occurring in grains like wheat, barley, and rye. The consumption of gluten by affected individuals is known to damage the lining of the small intestine which degrades the gut's nutritive function. For a comprehensive discussion of Celiac disease, please see **Celiac Disease: A Hidden Epidemic by Peter Green and Rory Jones (Collins 2006).** The consumption of gluten is known to lead to abdominal pain, weakness, dermatitis herpetiformus, cancer etc. The only cure for Celiac disease is to stop consuming gluten. Celiacs who exclude gluten from their diet experience improved health and vigor, usually within a few months. But it is very difficult to get gluten out of your life.

Gluten is present in the food supply for obvious reasons. It is naturally made by the fundamental grains of civilization, wheat, barley and rye. If you have some pizza and a beer---you're dining on gluten! But gluten is also a wonderful industrial tool, thickening sauces if wet, and in powdered form acting as a flow agent in dry ingredients. It is introduced into machines of production to support their smooth operation. As such gluten is nearly omnipresent in today's processed food supply. Companies that try to serve the market for Gluten Free foods take steps to ensure that their facilities and manufacturing ingredients are free of gluten. The FDA is currently developing food labeling guidelines in order set a federal standard for the term "Gluten Free," set to be released in mid 2008.

On August, 19 of 2005 the FDA held a **Public Meeting On: Gluten-Free Food Labeling** to organize and receive information from the public about Celiac disease. (A transcript of that meeting can be downloaded from the internet at the following URL- http://www.cfsan.fda.gov/~dms/glutran.html) The FDA heard testimony from biologists studying Celiac disease, scientists with knowledge of testing mechanisms for the presence of Gluten, agricultural experts, food manufacturers, and private citizens. Maryrose Hopke, representing the Celiac Disease Foundation testified that "two to three million consumers ...have to watch everything they eat and drink and every medication they take."[8]

Subsequently, the FDA determined that as Gluten represents a significant health risk to individuals with Celiac disease, with no standardized federal definition for labels, it would set a standard for use of the term "Gluten Free". This federal standard, to be set at no greater than twenty parts per million (ppm) of allowable gluten, was based on the sensitivity of the ELIZA assay, the current best test. The new standard for labeling will do away with the hodgepodge faced by consumers and manufacturers, trying to eliminate gluten from their food. The FDA will release its new regulations in mid-2008.

At this time there is no regulation limiting the use of gluten in prescription drugs or other medications. Individual manufacturers have the choice whether or not to make their product free of gluten. They can do so because gluten is on the FDA database of approved inactive ingredients for use in tablet form for oral usage(its CAS number is 008002800). But IPEC-Americas, an industry group representing excipient manufacturers has listed some of the most common other excipients now in use, at ipecamericas.org For a person with Celiac disease, any drug, prescribed or OTC, may or may not contain gluten, and considerable effort needs to be taken in determining the presence of gluten. This, even as there are many other excipients which could be substituted, cf. page 3. Some individuals, pharmacists, and Celiac support groups publicize lists of drugs that do not contain gluten. But these lists cannot take into account pharmacologically equivalent generics which are produced by different manufacturers, who may change their preparations without notice. Practically, what this means is that a person taking a generic risks being exposed to gluten because the manufacturer of their prescription has changed the excipient or that their pharmacy has

switched suppliers for business reasons.

To cite a personal example, I once took a generic drug only to start having reactions typical of a gluten exposure. To determine if I had had an exposure, I had to carefully review each and every food and medicine I had recently used, call the pharmacist to find out which generic manufacturer produced the medicine I had just taken, then call the manufacturer and search their database over the internet--Just to find out that they did not exclude gluten from this particular drug. But then I had to recover from my gluten exposure as well; a process that takes a couple weeks for me. As another example, I once suspected that a dose of Bayer brand aspirin had caused me to react to gluten. So I called Bayer to speak to their technical people, and found out that their aspirin is not manufactured in a Gluten-Free facility. In fact, gluten was being used in the same facility that made their aspirin.

If gluten were to be excluded from the safe inactive ingredient database, people like me could confidently take medicine. And those who do not have the resources to research every medication would be protected as well. We would not have to interrogate our pharmacists and drug manufacturers, and they in turn could safely and confidently dispense and produce medicines, without the added costs of tracking medications for Gluten. CVS and Drugstore.com do not keep a database of drugs that are gluten free.[9] For patients ordering drugs by mail it is not possible to be safe from Gluten, especially where generic prescriptions can be made by different manufacturers who may in turn vary their preparations from batch to batch. Drugs sourced overseas pose another significant layer of uncertainty. If wheat gluten were removed from the FDA list of GRAS excipients, pharmacists large and small would not bear the cost of determining which drugs in their formularies were gluten free, and consumers with celiac could confidently buy something as simple as generic aspirin and manufacturers would know that all their drugs were safe. Practically speaking, a patient could take generic aspirin for their heart without risking getting sick because there is gluten in the aspirin.

The FDA was created in 1938 after the tragic deaths of thousands of children had been found to be the result of an unsafe excipient, sulfanilamide. For 1% of the US population, Wheat Gluten is toxic. The FDA should revoke the safe inactive ingredient

classification of gluten as soon as possible for prescription drugs, both name brand and generic, and for OTC drugs as well. Wheat Gluten is currently classified as GRAS under 21 CFR 184.1322(d), a determination that dates back to the year 1958. Its use as an excipient is only permitted because it is generally recognized to be safe. 21 CFR330.1 (2)(e) requires excipents to be safe in the amounts administered. Gluten has no therapeutic effect. But gluten is toxic to people with Celiac disease, is not generally safe, and should no longer be included in the excipient database. The practical risk of cross-contamination during the manufacturing process means that the wheat gluten content of a batch of drugs is unknowable without specific testing similar to that which will be soon be required of foods in the United States.

If it is necessary for a particular drug to be made with wheat gluten, then labeling could be a reasonable remedy. Currently, people with phenylketonuria(PKU) benefit from warning labels on all packaging. They must avoid the artificial sweeter Aspartame, as it is made from aspartic acid and phenylalanine. But the number of people that cannot metabolize phenylalanine ranges from 1 in 14,000 to 20,000.[10] Celiacs represent 1% of the population who must avoid all gluten , whereas people with PKU avoid phenylalanine in order to minimize its concentration in the blood. As such, labeling the presence of wheat gluten in a medication could provide a remedy, if the standard could be reliable, and it was necessary for wheat gluten to be present in a given medication.

It is only through government regulation at the federal level that gluten can be eliminated from the supply of medications available today. Drug companies can and do substitute other inert agents as excipients in their products. Large and small pharmacies cannot efficiently track the presence of gluten in branded and generic pharmaceuticals. And consumers are at a significant disadvantage when drugs are prescribed to them or they go to purchase something as simple as an OTC analgesic. The FDA has already recognized the risk gluten in foods represents to a significant part of the US population and has determined that it is feasible to standardize the labeling of Gluten Free foods, including the necessary testing.

The FDA should reconsider the classification of gluten as a safe inactive ingredient. A uniform federal standard would be economically efficient since producers, distributers and patients could reliably and

at no cost know when wheat gluten is not present in their medications. Wheat gluten, like any excipient, must first be safe for the purposes intended. But wheat gluten must no longer be considered generally safe in the United States. Drugs taken for health reasons should be healthy for people with Celiac.

Claim for categorical exclusion from Environmental Impact statement

This petition does not require an Environmental Impact statement under Section 25.31 Human and Biologics (h) Issuance, revocation, or amendment of a standard for a biologic product.

The undersigned certifies, that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which are unfavorable to the petition.

Michael Weber

[1] From an email contact to CVS below;

Dear CVS Customer,
Thank you for contacting CVS.com.
Unfortunately, we do not access to computer systems used by local CVS/pharmacies and cvs.com pharmacy at this location; therefore, I am unsure if the CVS system is able to flag medications for gluten content. Pharmacy representative at your local CVS/pharmacy or Customer Care representative at cvs.com pharmacy at (888) 607-4287 may be able to provide you with more information.
In general, very few manufacturers can guarantee that their drug is free from wheat, barley, rye and oats derived products, ingredients that can aggravate celiac disease. Upon our research, we've found that manufacturers cannot prevent cross-contamination with other gluten-containing products and are likely to change the medication's formulation without any notice. So, variations are likely from batch to batch. Therefore, we recommend that you or your pharmacist check the gluten content of their products periodically by calling the manufacturer directly with the batch number. They may be able to tell you if the product you will receive is gluten free.
I hope this meets your needs. Please feel free to contact us if you need further assistance or if you have any other questions.
Sincerely,
Sunghee B., PharmD

[2] IPEC-Americas website

[3] From my conversation with Stu Levine at Teva on 2/27/08

[4] CVS email

[5] Lee, Anne Roland et al. "The Economic Burden of a Gluten Free Diet." Journal of Human Nutrition and Dietetics. 2007 October:20(5): 423-30.

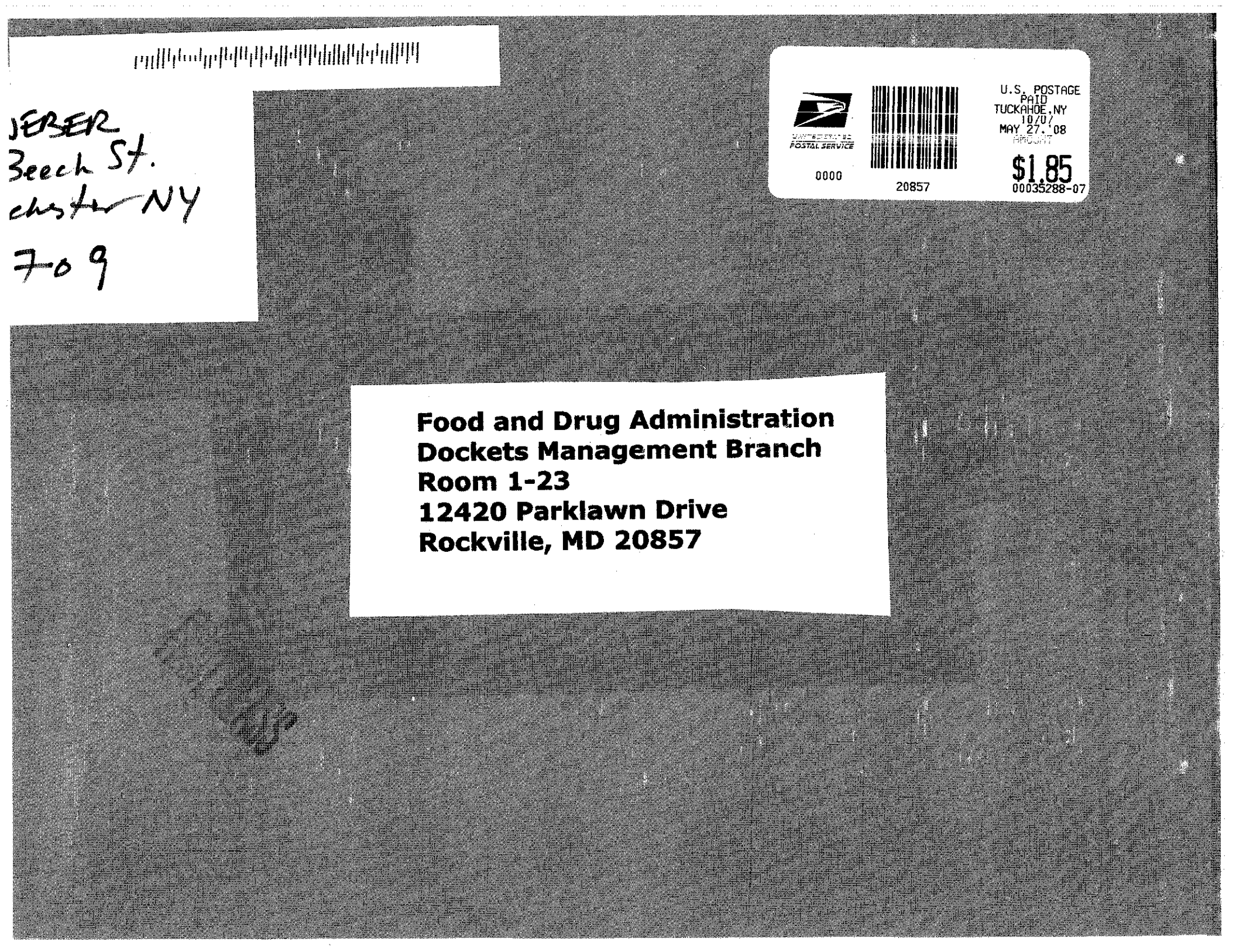
[6] FDA panel on gluten free labeling- http://www.cfsan.fda.gov/~dms/glutran.html

[7] Columbia University Celiac Disease Center website

[8] From the **PUBLIC STATEMENTS** portion of FDA panel

[9] From my own phone conversation with Brian of Drugstore.com on 2/26/08. I do not know this gentleman's surname.

[10] Rezvani I (2004). Phenylalanine section of Defects in metabolism of amino acids. In RE Behrman et al., eds., Nelson Textbook of Pediatrics, 17th ed., chap. 74, pp. 398–402. Philadelphia: Saunders.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