January 15, 2007

Food and Drug Administration (FDA)
Office of the Ombudsman
Food and Drug Administration
5600 Fishers Lane
Room 14B03, HF-7
Rockville, MD 20857

Subject: Information Quality Appeal per the HHS Information Quality Guidelines

Dear Sir or Madam,

I am writing per the HHS Information Quality Guidelines to appeal the denial (dated December 15, 2006, postmarked December 20, 2006) of my request that information be corrected in the following documents:

Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food March 2006. http://www.cfsan.fda.gov/~dms/alrgn2.html (hereafter referred to in my letter as the "Thresholds Report").

FDA's Responses to Public Comments on the Draft Report "Approaches to Establish Thresholds for Major Food Allergens and for Gluten in Food" March 2006. http://www.cfsan.fda.gov/~dms/alrgcom.html

I've attached a copy of my original request (Attachment A) and of FDA's response (Attachment B) as PDF file attachments to my transmittal email.

Below are the specific reasons why the Agency response is inadequate:

1. **FDA's assertion that "the purpose of Threshold Report was not to decide whether to establish any thresholds for allergens, to prescribe the use of any specific approach if a decision were made to establish any such thresholds, or to suggest any specific threshold values" is inadequate to prevent misuse of the faulty information in the report.**

A common thread of FDA's response letter, both in the background information and in the specific responses, is the assertion that, because the Threshold Report includes

caveats that the report is not definitive and that the assumptions might be re-examined in the future, no corrective action is needed.

However, while it is true that report does include such caveats, such statements can easily become lost over time. Particular in areas where there is a dearth of information, such as is the case with food allergen thresholds, findings from a scientific, peer-reviewed study by a reputable agency like FDA will inevitably become the "default" assumptions. Secondary references will quote the findings without the caveats, and tertiary references may not even include the original citation.

Such an assertion may sound far-fetched, but in fact it has already begun. FDA's guidance to industry on the labeling for certain uses of soy lecithin states that "FDA considers an 'adverse effect' to be <u>any objective sign</u> of an allergic reaction," (emphasis added) and then cites the Threshold Report as a source.[1] However, the Threshold Report makes no such statement, and in fact includes many careful caveats about how there is no clear consensus on which biomarkers, including subjective symptoms, should be used in determining what is an adverse effect for the purposes of establishing thresholds.

In my comments to the draft Threshold Report, I argued that, for the purpose of labeling, subjective symptoms (e.g., nausea, abdominal pain, chest pain, dizziness) should be considered an adverse effect, particularly due to the fact noted in the thresholds report that a given dose might elicit a mild symptoms one day and life-threatening reactions the next, and that in some cases the "initial objective sign" has been death.

However, when FDA declined to make any changes to the report in response to my comment, I did not include it in my information quality challenge, because I thought the report adequately presented both sides of the argument.

Yet only <u>one month</u> after the Threshold Report was finalized, all the nuanced discussion on biomarkers was ignored and the report's "recommendation" on using "initial objective sign" was presented as a final decision in the FDA guidance document on soy lecithin.

In other words, I don't believe FDA's assertion that they won't present the information in the Thresholds Report as a final decision without further evaluation, because they have already done so.

2: FDA's responses to my concerns about a specific statement on the uncertainty factor do not address the central issue

My initial information quality correction request challenged the following specific statement on page 48 of the report:

[1]FDA *Guidance on the Labeling of Certain Uses of Lecithin Derived from Soy Under Section 403(w) of the Federal Food, Drug, and Cosmetic Act*, (Section B) April 2006. see http://www.cfsan.fda.gov/~dms/soyguid.html

"Based on currently available data, the Threshold Working Group was unable to identify any scientifically-based studies that indicate that the standard 10-fold uncertainty factor used in safety assessments for inter-individual variability is not adequate to account for variation within the sensitive population."

My request characterized this statement as "lacking in both utility and objectivity." Perhaps it would have been better to just explain that I view the statement as untrue. The Threshold Working Group was able to identify at least three scientifically-based studies that indicated that the standard 10-fold uncertainty factor might not be adequate to account for variation within the sensitive population. On page 23 of the Threshold Report, FDA cites three studies showing there may be a range of as much as one-million-fold in eliciting doses from the least sensitive to the most sensitive individuals.

In their response to my challenge, FDA does not address this contradiction (i.e., the statement saying that FDA was unable to identify any studies and an earlier citation of three studies). It is important to note that the two contradictory statements are separated in the report by twenty-five pages – in other words, the discussion of safety factors does not even acknowledge the million-fold range that was noted earlier in the report.

Instead, FDA's response points out that the discussion included the following caveat:

"However, because of limitations in the clinical studies and the case reports discussed above, this assumption should be reexamined as more data on the distribution of sensitivities within the population becomes available."

Unfortunately, a recommendation to reexamine an assumption in the future does not in any way address the fact that the assumption is known to be flawed today. To use an overly facile hypothetical example, if FDA were to produce a report that said, "Based on currently available data, the Tobacco Working Group was unable to identify any scientifically-based studies that indicate a link between smoking and lung cancer," it wouldn't matter how many caveats and promises to reexamine this assumption as more data were made available were added.

It is important to note that I am not claiming that the 10-fold assumption is clearly inadequate, just that the currently available scientific data indicate that it may be inadequate. As I discussed in my initial challenge, this assertion is supported by the report of the Food Advisory Committee (FAC) (July 15, 2005 transcript at pages 24-25):

"'IgE-mediated allergic reactions essentially are amplifiers. They amplify reactions to minute amounts of allergens. So the application of uncertainty factors to thresholds on the double-blind, placebo-controlled, food challenge may not be sufficiently large to handle this variation of amplifications of an allergic response." (emphasis added)

FDA's response states that this FAC statement "is consistent with the Thresholds Report and the sentence [I] challenge in [my] letter." However, the response fails to explain how the FAC sentence stating that the uncertainty factor may not be large enough is consistent

with the Thresholds Report statement saying that there is no scientific that the standard uncertainty factor is not adequate. The two statements seem contradictory to me.

Instead, the FDA response produces additional quotes from the FAC report, stating the uncertainty factor is unknown (I don't disagree), that the uncertainty factor be informed by the distribution of NOAELs and LOAELs (if such a distribution were available I would also agree), and that if reproducible, subjective responses in patients with a history of life-threatening anaphylaxis are included, the uncertainty factor might be lower than 10 (again, if such data were available, I wouldn't disagree).

However, none of these statements would seem to support the statement that is the subject of my challenge.

In summary, in their response FDA has failed to directly address the fact that there is scientific evidence that, based on currently available data, the standard 10-fold uncertainty factor for inter-individual variability may not be adequate to account for variation within the sensitive allergic population.

2. FDA's decision to selectively discard data on non-detects is inexcusable.

I am baffled by FDA's decision to defend the Threshold Report's practice of discarding data on non-detects when calculating the "hypothetical" threshold for the statutory-derived approach. In their response, FDA clarifies that only "some, but not all, data from five, not four, studies were excluded." Frankly, this supposed defense of the report is even worse than my assumption that whole studies were discarded. If a study was determined adequate for inclusion, then all the data should have been included.

Instead, FDA points out that "a finding of protein was not detected does not necessarily indicate that it was absent." I don't disagree, which is why it is standard practice to count "non-detects" at half the detection limit, which is given for at least two of the studies (<0.3 ng/ml *Peeters et al*., 2004 and 0.4 mg/kg, *Yeung and Collins*, 1996). If a detection limit was not made available, then I would assert that including any of the data is inutile. Selectively excluding non-detects has the effect of severely skewing the data, producing a "hypothetical" threshold level much higher than would otherwise be calculated.

3. FDA incorrectly asserts that the Thresholds Reports discussion on a "lack of data" on oils for the statutory approach encompasses the data issues identified by the FAC.

In my correction request, I ask that the Thresholds Report be revised to include the limitations of the statutory approach that had been identified by the FAC. FDA's response is that the current discussion of a "lack of data" encompasses all the limitations identified by the FAC.

However, two of the limitations identified by the FAC had nothing to do with a lack of data, but rather spoke to inherent limitations of extrapolating protein levels in oil to

protein levels in other food. These are limitations that no amount of data on proteins in oil can address.

The first is the denaturation and changes in the conformational epitopes that occur in oil. In other words, the proteins found in oils are not the same as proteins found in other foods and therefore cannot be assumed to have the same allergenic effect. This limitation is a major flaw in the statutory approach that no amount of additional data can rectify.

The second is the matrix effect (fat levels), which can affect the dose level needed for an adverse response. In other words, protein found in oils does not behave in the same manner as protein found in other foods. This limitation is a second major flaw in the statutory approach that no amount of additional data can rectify.

FDA's response asserts that these two limitations "are not directly related to the description of the strengths, weaknesses, and data needs of that approach." I believe that a consensus finding by the FAC that "levels of protein in oils did not apply to all food allergens" is directly related to the major weakness in the statutory approach and the specific reasons behind that FAC finding should be documented in the report and not hidden behind a discussion of a "lack of data."

4. **FDA's defense of the Thresholds Report finding that the statutory approach might yield thresholds that are "unnecessarily protective of public health" does not address the fact that the limitations identified by FAC would lead to the opposite conclusion**

To my mind, a major finding in an FDA report that an approach might be "unnecessarily protective of public health" could only be made if all scientific information pointed to those thresholds being overly protective. However, the two limitations that the FAC identified (denaturation and matrix effects) would lead to the opposite conclusion.

Once again, FDA defends a faulty statement by pointing out that it is followed by caveats and a recommendation to "reevaluate" as more information is available. And once again, these caveats and promises to reexamine an assumption in the future does not in any way address the fact that the assumption is known to be flawed today.

FDA's response also notes that the FAC report suggests that use of a threshold data for a single allergen to establish thresholds for other allergens might prove too restrictive. This statement is something of a red herring. My expressed concern was not extrapolating levels of protein in peanut oil to other allergens, but rather extrapolating levels of protein in peanut oil to other peanut-containing foods. If FDA wishes to keep the language about the statutory approach being "unnecessarily protective," then it should be amended to make clear that the only aspect that might be unnecessarily protective is the extrapolation of one allergen to another, and that the extrapolation of protein levels in oil to protein levels of the same allergen in other foods may not be protective due to denaturation and matrix effects.

Thank you very much for taking the time to seriously consider my requests. I realize that revising a major report after it has been finalized is no small task, but give the influence this report is likely to have, I feel it is imperative that it meets data quality standards.

Please feel free to contact me if you have any questions.

Sincerely,