DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

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Re: Docket 2005FL-0488

Dear Ms. Barry and Dr. Reddy:

This is in regard to the notification jointly submitted on November 23, 2005 by International Media and Cultures, Inc. (IMAC) and F & A Dairy of California, Inc. (F & A Dairy) in accordance with section 403(w)(7) of the Federal Food, Drug, and Cosmetic Act (the Act). IMAC is a manufacturer of starter culture media that are used to grow starter cultures. F & A Dairy is a manufacturer of cheeses made with starter cultures grown in IMAC starter media. FDA received correspondence from F & A Dairy on November 16, 2005 that was not designated as a notification for exemption for allergen labeling. On November 23, 2005, FDA received a joint submission from IMAC and F & A Dairy clearly designated as a notification. FDA incorporated the earlier correspondence from F & A Dairy into the joint notification, and considers the notification to have been received on November 23, 2005. The notification has been designated FALN 003.

According to the statement of purpose in a memorandum prepared by IMAC and submitted with the notification, this notification is intended to inform FDA of the view that the hydrolyzed soy solids[1] used as an ingredient in IMAC's starter media are exempt from food allergen labeling requirements and thus need not be declared on the label of cheese and other dairy products produced using bulk starter cultures containing these soy solids. According to FALN 003, hydrolyzed soy solids have undergo thermal, enzymatic, and acid hydrolysis during production of starter media, production of starter cultures, and

[1] The term "hydrolyzed soy solids" employed by the notifiers is here used only for the purpose of responding to this notification and should not be considered an endorsement of a particular common or usual name for this ingredient.

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production and storage of cheese. FALN 003 contends that, as a consequence of this hydrolysis, the soy proteins originally present in the starter media are rendered into non-allergenic hydrolyzed soy solids.

The notification presents information on the evolution of dairy starter cultures; a description of how hydrolyzed soy solids are made and subsequently used in the starter culture media and how the starter culture media are used to make bulk starter cultures that are used in cheese-making; statements from physicians and medical professors giving opinions on the lack of adverse reactions from the consumption of cheese that contain starter cultures made with hydrolyzed soy solids; and statistical data on the amount of cheese made with bulk starter cultures using IMAC starter culture media containing hydrolyzed soy solids.

In part, FALN 003 argues that cheese and other dairy products made with IMAC starter culture media may be safely consumed by soy allergic consumers. However, under section 403(w)(7), a notifier must demonstrate that the ingredient that is the subject of the notification does not contain allergenic protein.[2] There is an alternative process (a petition process under section 403(w)(6)) by which a person may request that an ingredient be exempt from the allergen labeling requirements in section 403(w)(1); the standard for exemption under this alternative process is that the petitioner must provide scientific evidence (including the analytical method used to produce the evidence) that demonstrates that the food ingredient (as derived by the method specified in the petition) does not cause an allergic response that poses a risk to human health. Importantly, FALN 003 was submitted as a notification under 403(w)(7) and thus the notification must demonstrate that the ingredient does not contain allergenic protein.

FDA objects to FALN 003 because the notification fails to provide scientific evidence (including the analytical method used) that demonstrates that the soy solids[3] (as derived by the method specified in the notification) do not contain allergenic protein, as required by section 403(w)(7). FALN 003 neither provides sufficient scientific evidence to determine that soy solids do not contain allergenic protein, nor does FALN 003 otherwise meet the requirements of section 403(w)(7).

The notification asserts that the soy solids do not contain allergenic soy proteins because, during production of starter culture media, preparation of bulk starter cultures at the cheese plant, cheese making, and the storage of the finished cheese, the soy solids present in the culture media undergo a series of thermal, enzymatic, and acid hydrolyses that break the proteins into smaller peptides and amino acids, which, the notification claims, renders the soy protein non-allergenic. The notification asserts that during the process of making the starter culture media, cellulase and protease present in the culture media will

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[2] Alternatively, a notification may contain a determination by FDA that the ingredient in question does not cause an allergic response that poses a risk to human health under a premarket approval or notification program under section 409 of the act. FALN 003 contains no such determination.

[3] The notification states that the ingredient that is the subject of this notification is hydrolyzed soy solids. However, in the description of the manufacturing process, the notification states that the starting ingredient is soy flour. In the absence of evidence demonstrating that the soy solids in the soy flour are completely hydrolyzed, FDA believes that it is more appropriate to refer to the ingredient as "soy solids."

act on soy flour and the protease will digest soy proteins to smaller peptides. The notification further asserts that, after the culture media are inoculated with various bacterial strains suitable for production of cheese and other dairy products, the bacteria secrete proteases that would hydrolyze the denatured soy proteins. IMAC claims that during bacterial fermentation, as well as during manufacturing of dairy products, any remaining soy proteins would be hydrolyzed.

FALN 003 does not include any studies or other data to provide evidence supporting the claims that the soy solids are completely hydrolyzed. In addition, IMAC starter culture media could be used with different types of bacterial cultures and in the manufacture of different types of cheeses. The degree of hydrolysis obtained would vary depending on the types of cultures used and the conditions used in the fermentation of the bulk starter culture itself and perhaps even the conditions of manufacture of the cheeses themselves. However, the notification provides no information on the variation in hydrolysis resulting from the use of different types of starter cultures, different means of bulk starter culture preparation (i.e., the fermentation conditions), and differences in the manufacture of various cheeses. In addition, although the request for exemption under FALCPA refers to use of the starter cultures grown in IMAC starter culture media in cheese and other dairy products, the notification provides no information or data on the use of the starter cultures in any dairy products other than cheeses.

Although the notification describes how the starter culture media are made, it does not characterize the starter culture media or the hydrolyzed soy component. For example, the notification does not provide information on the amount of soy protein present at any point during the production of the culture media, production of the starter culture, or utilization of the starter culture in cheese or other dairy products. In addition, there are no data presented on the peptide length profiles of the soy protein at any of these points.

The notification also includes, as an addendum, a summary of results from radioallergosorbent test (RAST) testing of mozzarella cheese products. The notification states that the tests were conducted at the National Jewish Hospital (NJH) in Denver, Colorado. Based on a summary of the NJH results, the notification asserts that: 1) mozzarella cheese prepared with the starter culture fermented in the starter media containing heat-treated soy proteins contained a significantly lower level of soy allergens than the starter media used as a positive control; 2) mozzarella cheese prepared with the starter culture fermented in the IMAC starter media did not contain soy allergens; and 3) mozzarella cheese prepared with the starter culture fermented in the starter media formulated without soy proteins did not contain soy allergens. However, the notification does not present a validated, quantitative IgE assay demonstrating that the soy solids do not contain allergenic soy protein. Moreover, the notification provides no description of the methodology, detection limits, number of test samples, controls, and origin of the sera used. The notification also does not include any of the actual data generated during the testing. The notification cites an article by Dolen[4] for the details of the testing procedure. However, this reference is a review article of several commercially available assays to detect IgE, and the notification does not indicate which one of these, if any, was used in

[4] W.K. Dolen. The Diagnostic Allergy Laboratory.

the NJH testing. Further, the article describes assays for detecting antibodies in patient serum, not for assays using antibodies to measure allergenic protein in food or food ingredients, which is the test more relevant to the question presented by FALN 003.

The notification includes several communications sent to FDA and the California Department of Food and Agriculture (CDFA) in which the notification asserts that regulatory officials verified "the non-allergenic view of hydrolyzed soy in the wake of various treatments that it undergoes during starter making, cheese making and storage." However, the notification contains no response from FDA or CDFA stating either agency's view that the soy solids in starter cultures used to make cheese do not contain allergenic soy protein.

FALN 003 also alludes to inspections by regulatory agencies; the notification claims these inspections show that there were no allergens found in cheese made with starter cultures made from starter culture media containing soy solids. However, the notification does not provide a description of any analytical tests conducted by any regulatory agency or any results of such testing. In addition, the notification provides statements from physicians and medical professors, which assert that there have not been reports of allergic reaction to cheese made with IMAC starter cultures. In any event, the lack of regulatory action on the part of FDA or CFDA and the absence of reports of allergic responses are not scientific evidence that demonstrates the absence of allergenic protein in the soy solids used in IMAC starter media.

Conclusion

FALN 003 asserts that hydrolyzed soy solids used as an ingredient in IMAC's starter media are exempt from food allergen labeling requirements and thus need not be declared on the label of cheese and other dairy products produced using bulk starter cultures containing these soy solids. But FALN 003 does not contain scientific evidence (including the analytical method used) that demonstrates that soy solids (as derived by the method specified in the notification) do not contain allergenic protein, as required by section 403(w)(7). FALN 003 neither provides scientific evidence to determine that soy solids do not contain allergenic protein, nor does FALN 003 otherwise meet the requirements of section 403(w)(7). FDA therefore objects to FALN 003.

Sincerely yours,

Scott Gottlieb, M.D.
Deputy Commissioner
for Medical and Scientific Affairs