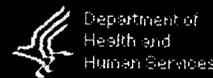


ATTACHMENT-6



U.S. Food and Drug Administration



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January 23, 2006

Agency Response Letter - Objection Regarding Extensively Hydrolyzed Casein FALN No. 002 (Docket No. 2005FL-0434)

Pamela Anderson, Ph.D., RD
Director, Regulatory Affairs
Ross Products Division
Abbott Laboratories
625 Cleveland Avenue
Columbus, Ohio 43215-1724

Dear Dr. Anderson:

This is in regard to the notification dated October 21, 2005 that Ross Products Division of Abbott Laboratories (Ross) submitted in accordance with section 403(w)(7) of the Federal Food, Drug, and Cosmetic Act (the Act). FDA received the notification on October 26, 2005 and designated it as FALN 002.

The subject of FALN 002 is Ross' extensively hydrolyzed casein (EHC)^[1], derived from cow's milk (milk). FALN 002 informs FDA of Ross' view that based on scientific evidence, EHC does not contain allergenic protein from milk. Ross' EHC is used in infant formulas marketed as hypoallergenic and is intended for milk-allergic infants.

As part of its notification, Ross includes a discussion of the legal basis for filing a notification under the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA), a description of Alimentum (the infant formula in which the ingredient is used), a description of the manufacture of EHC and of Alimentum, scientific data purportedly demonstrating that the product does not contain allergenic protein, and the analytical method used to demonstrate that the product does not contain allergenic protein. Ross also includes various references that address food allergy in infants, the use of hypoallergenic infant formulas, and milk allergy generally.

FDA objects to FALN 002. FALN 002 does not contain sufficient scientific evidence (including the analytical method used) that demonstrates that EHC (as derived by the method specified in the notification) does not contain allergenic protein, as required by section 403(w)(7) of the Act. FALN 002 neither provides sufficient scientific evidence to determine that EHC does not contain allergenic protein nor does FALN 002 otherwise meet the requirements of section 403(w)(7).

An ingredient that does not contain allergic protein would not be expected to provoke clinical reactivity in

allergic individuals. FALN 002 includes references demonstrating clinical reactivity to EHC-containing Alimentum. However, Ross does not explain why this evidence of clinical reactivity to EHC-containing Alimentum, as described in the cited references, does not contradict its assertion that EHC does not contain allergenic protein. In addition, the evidence presented in the notification is insufficient to demonstrate that EHC does not contain protein that binds immunoglobulin E (IgE), and the characterization of EHC is inadequate.

Characterization of EHC

Ross' assertion that EHC does not contain allergenic protein relies on the fact that the ingredient is enzymatically digested, thereby reducing its allergenicity by transforming intact casein into very small peptide fragments. But Ross does not demonstrate that the enzymatic digestion of casein, a known allergen, results in a hydrolyzed casein that is not allergenic. In fact, Ross provides minimal information regarding the method and extent of hydrolysis of EHC. Ross did not provide sufficient information regarding the manufacturing process of the ingredient, such as the source and composition of the starting material; the characterization of the enzyme used to carry out the hydrolysis; the actual digestion conditions; the inactivation method used; the molecular weight cut-off for, or conditions during, the filtration process; the criteria and methods for post-digestion processing; and information on batch-to-batch variation for any of these conditions. In one of the references in the notification (Cordle *et al.*, 1991), data are provided on the molecular weight distribution of several lots of EHC. The data show that 1.7% of the casein hydrolysate material had molecular weights in the range of 1200 to 1500 daltons. This range corresponds to peptides of approximately 9 to 15 amino acids in length and may therefore represent immunogenic protein.

Ross cites two references (Cordle *et al.*, 1991 and Cordle *et al.*, 1994) describing the ELISA procedure used to test the EHC. One of these references (Cordle *et al.*, 1994) further describes the ELISA assay as a method to characterize EHC-containing infant formulas. Ross indicates that the firm uses a modification of the procedure described in these two references to ensure that the EHC meets or exceeds the standards necessary to produce a hypoallergenic finished product. However, in the notification, Ross does not describe the modification used or the specificity of the ELISA assay. Nor does Ross present information on how this ELISA assay is used during the manufacture of the infant formula to ensure quality. For example, there are no data on what material is sampled, how the test material is prepared, what level of accuracy is obtained, or what standards are used. There are also no data on the results of this testing, including batch-to-batch variation. Further, the assay appears to use polyclonal antibodies against intact casein (Cordle *et al.*, 1991). Ross provides no evidence demonstrating the efficacy of these antibodies for detecting partially degraded, but still allergenic, protein. Thus, the results presented in Table 1 of the Cordle *et al.* reference (Cordle *et al.* 1994) showing differences in the amount of "immunologically active" casein in formulas containing whole milk, partially digested casein, and extensively digested casein could reflect the level of intact (undigested or lightly digested) protein. Moreover, ELISA data from Cordle *et al.* (1994) and Sampson *et al.*, (1991) show that, in addition to low but detectable levels of casein, detectable levels of whey protein, another source of milk allergen, were also present. There is no discussion by Ross of the potential clinical significance of these residual casein or whey proteins.

Immunogenicity and IgE Binding

In vivo immunological assays in animals may be used to describe immune responses to specific proteins. However, these models have methodological flaws and are not widely recognized as sufficient scientific evidence that a protein is not immunogenic in humans and at best currently provide supplemental preclinical information (Kimber *et al.* 2003). Ross cites two studies using a rabbit model system (Cordle *et al.*, 1991 and

Cordle *et al.*, 1994) and one using a guinea pig model (Cordle 2004). Although all three studies show that EHC produced smaller responses than intact casein, some immunogenic activity was detected. In each case, the overall value of these animal studies for establishing the absence of allergenic protein in an ingredient is summarized by Cordle *et al.* (1994), who state that when using this model, a negative result would not prove hypoallergenic performance.

IgE binding and responses are also an important component of evaluating the allergenicity of an ingredient. Ross provides very little evidence in the notification to demonstrate that EHC does not bind IgE in sensitive individuals. In fact, some supplemental references provided by Ross demonstrate by in vitro RAST or in vivo skin prick tests (SPT) that EHC-containing Alimentum directly binds IgE (Sampson *et al.* 1991, Oldaeus *et al.*, 1991). In addition, there are literature references not cited by Ross that show evidence of IgE-binding to Alimentum (Schwartz *et al.*, 1991, Ragno *et al.*, 1993). Although demonstration of IgE binding does not necessarily predict clinical reactivity, this finding suggests that Alimentum contains proteins that may be allergenic.

Allergenicity

Ross' assertion that EHC does not contain allergenic protein also relies on the fact that the EHC-containing infant formula, Alimentum, has been demonstrated to be a "hypoallergenic" infant formula. This evidence is demonstrated through controlled clinical studies in humans. Ross cites one study by Sampson *et al.*, (1991) to demonstrate that a formula containing EHC meets the American Academy of Pediatrics (AAP) definition for hypoallergenic infant formulas. AAP defines hypoallergenic as a statistical probability with 95% confidence that at least 90% of allergic individuals will not react to the formula. However, evidence that an EHC-containing formula is hypoallergenic does not establish that a product does not contain allergenic protein because, as pointed out by Sampson *et al.*, hypoallergenic does not mean nonallergenic. In fact, included in the notification and in medical literature not cited by Ross are documented reports of adverse reactions to Ross' extensively hydrolyzed hypoallergenic product, Alimentum (Oldaeus *et al.*, 1991, Ragno *et al.*, 1993, Schwartz *et al.*, 1991, Hoffman *et al.*, 1997). Further, the AAP states that hypoallergenic products can still cause adverse reactions in sensitive individuals (AAP 2000) and Ross acknowledges in the notification on page 5 that "there is a very small number of exquisitely sensitive milk-allergic infants who will not be able to consume a hypoallergenic infant formula." In the case of Alimentum, these statements are evidenced by data from two studies Ragno *et al.* and Oldaeus *et al.*, in which double-blind placebo controlled food challenge with Alimentum in milk sensitive individuals identified reactors in 2 out of 20 and 1 out of 11 individuals, respectively. These results demonstrate that EHC-containing Alimentum contains proteins that are capable of eliciting allergic responses in milk-allergic individuals.

Previous Review Under 409

Ross concedes in FALN 002 that the EHC used in Alimentum has not been reviewed under the provisions of section 409 of the Act. However, Alimentum has been the subject of a premarket notification under section 412, through which Ross submitted data and information supporting the marketing of Alimentum as a hypoallergenic infant formula. Ross contends that "FDA reasonably concluded as part of its review under section 412 that Alimentum would not cause an allergic response that poses a risk to human health." Ross therefore urges FDA to conclude that its review of Alimentum under section 412 is tantamount to a finding under section 409 that Alimentum does not cause an allergic response that poses a risk to human health, and that Alimentum is thus exempt from the labeling requirements of section 403(w) pursuant to section 403(w)(7)(A)(ii). FDA disagrees.

FDA did not object to the premarket notification for Alimentum under section 412, but this does not mean that FDA concluded that Alimentum does not cause an allergic response that poses a risk to human health. As noted, the fact that a product is hypoallergenic does not mean that the product is nonallergenic, and that fact should not be used as evidence to demonstrate that the product does not contain allergenic protein. In fact, there is evidence that Alimentum containing EHC induces allergic responses in sensitive individuals and thus contains allergenic protein.

Conclusion

Ross notifies FDA in FALN 002 that EHC does not contain allergenic protein. In FDA's view, FALN 002 does not contain scientific evidence (including the analytical method used) that demonstrates that EHC (as derived by the method specified in the notification) does not contain allergenic protein, as required by section 403(w)(7) of the Act. FALN 002 neither provides sufficient scientific evidence to determine that EHC does not contain allergenic protein nor does FALN 002 otherwise meet the requirements of section 403(w)(7). FDA therefore objects to FALN 002.

Sincerely yours,

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

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Note

[1] The term "extensively hydrolyzed casein" employed by the notifier 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 Ross' ingredient.

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