

Doclet 2005N-0416



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

0602 '06 MAR 28 10:03

Food and Drug Administration
College Park, MD 20740

Mr. Matias Diez
Manager, Regulatory Affairs
Mead Johnson Nutritionals
2400 West Lloyd Expressway
Evansville, IN
47721-0001

December 27, 2005

Dear Mr. Diez:

This is in regard to the notification dated September 29, 2005 that Mead Johnson Nutritionals (Mead Johnson) submitted in accordance with section 403(w)(7) of the Federal Food, Drug, and Cosmetic Act (the Act). FDA received the notification on September 30, 2005 and designated it as FALN 001.

The subject of FALN 001 is Mead Johnson's extensively hydrolyzed casein (EHC), derived from cow's milk (milk).¹ FALN 001 informs FDA of Mead Johnson's view that based on scientific evidence EHC does not contain allergenic protein from milk. Mead Johnson's EHC is intended for use in infant formulas marketed as hypoallergenic for milk-allergic infants.

As part of its notification, Mead Johnson includes a discussion of the history of use of the ingredient, descriptions of the products in which the ingredient is used, a method of manufacture, a method for detection of casein antigenicity, and distribution profiles of its EHC by peptide length and molecular weight. Mead Johnson also includes various references that address food allergy in infants, the use of hypoallergenic infant formulas, characterization of EHC, and milk allergy generally.

FDA objects to FALN 001. FALN 001 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). FALN 001 neither provides sufficient scientific evidence to determine that EHC does not contain allergenic protein, nor does FALN 001 otherwise meet the requirements of section 403(w)(7).

FALN 001 does not address the evidence of clinical reactivity to EHC by milk-allergic patients contained in the references provided by the notification. FALN 001 also does not address the evidence of clinical reactivity to Mead Johnson's EHC that is readily available in the literature. An ingredient that does not contain allergenic protein would not be expected to provoke clinical reactivity in allergic individuals. 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.

¹The 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 Mead Johnson's ingredient.

2005N-0416

ANS 1

EHC Allergenicity

Clinical evidence of allergic responses to a food or food ingredient strongly suggests that allergenic protein is present in that food. The evidence provided by Mead Johnson suggests that allergic responses occur in some milk-allergic individuals exposed to EHC. Additionally, Mead Johnson fails to address readily available evidence in the literature documenting such responses to its EHC (Lifschitz et al., 1988; Bock, 1989; Saylor and Bahna, 1991; Schwartz, 1992; Hill et al., 1995; Hoffman and Sampson, 1997).

In support of its notification, Mead Johnson cites a number of studies with EHC formulas in infants that do not have milk allergy. These studies are not relevant to question of whether this EHC contains protein that is allergenic for milk-allergic individuals.

Mead Johnson also provides evidence that EHC formulas (including Mead Johnson EHC formulas) are widely used for the management of infant milk allergy and are generally considered "hypoallergenic." The American Academy of Pediatrics (AAP) defines "hypoallergenic" to indicate 95% confidence that 90% of allergic individuals will not react to a given formula. The studies cited by Mead Johnson that show decreased clinical symptoms in response to the substitution of EHC formulas for milk-based formulas are consistent with the claim that EHC is hypoallergenic.

However, demonstrating that EHC is hypoallergenic does not establish that EHC does not contain allergenic protein. The AAP recognizes the risk of reaction from extensively hydrolyzed formulas in some sensitive individuals and other national and international groups have recommended exercising caution when using these formulas. Recent references cited by Mead Johnson in the notification also acknowledge that some individuals may show allergic symptoms to extensively hydrolyzed formulas and may require amino acid (elemental) formulas. And there is other evidence that individuals with cow's milk allergy have experienced allergic reactions upon consuming formula containing Mead Johnson's EHC, with some reactions being reported as severe (Lifschitz et al., 1988; Bock, 1989; Saylor and Bahna, 1991; Schwartz, 1992; Hill et al., 1995; Hoffman and Sampson, 1997). None of this evidence is discussed in the notification.

IgE Binding and Immunogenicity of EHC

The clinical evidence demonstrating that EHC can provoke allergic reactions undercuts information in the notification that is intended to demonstrate that EHC does not contain allergenic protein. However, even in the absence of such clinical evidence, FDA notes that there are significant deficiencies in the evidence provided by Mead Johnson on the IgE binding activity and immunogenicity of its EHC.

Mead Johnson cites a crossed radioimmuno-electrophoresis (CRIE) study as evidence that IgE produced by milk-allergic individuals does not bind to EHC. However, the CRIE method used in the study is outdated and relatively insensitive, as acknowledged by the study authors who state that "the lack of CRIE scores does not necessarily reflect a complete lack of allergenicity." More recent studies have demonstrated *in vitro* IgE binding to Mead Johnson's EHC by modern analytical methods (Dean et al., 1993; Hoffman and Sampson, 1997; Docena et al., 2002). This evidence was not addressed by the notification.

Skin prick tests are generally considered an indicator of the presence of serum IgE rather than an absolute diagnosis of clinical allergy. Mead Johnson cites a study in which five milk-allergic children challenged with EHC by skin prick test did not react. However, the authors of that study

state that all subjects had previously tolerated a Mead Johnson EHC formula. Given this information, it is not surprising that no reaction to the skin prick test was seen. Other studies have reported individuals with positive skin prick tests in response to challenge with Mead Johnson's EHC (Bock, 1989; Saylor and Bahna, 1991; Sampson et al., 1991; Schwartz, 1992; Hill et al., 1995). This evidence was not addressed by the notification.

The sensitization study in guinea pigs presented by Mead Johnson did not contain sufficient information to enable FDA to assess the significance of the results. The study does not state the number of animals used, the amount of EHC used in attempts to induce sensitization or reaction, or the sensitivity of the assay used to measure induction of specific antibodies. In addition, Mead Johnson has not established that the guinea pig is a validated model for studying allergenic potential in humans. In fact, no validated animal model of allergenic potential in humans exists at the present time (Kimber et al., 2003). Therefore, such animal studies of immunogenicity may inform, but currently cannot replace, clinical evidence.

Characterization of EHC

Establishment of the identity of an ingredient and whether it contains allergenic protein requires adequate specifications for the ingredient, a sufficiently detailed method of its derivation, and information about the sensitivity and limitations of the methods used for analysis. FALN 001 does not adequately characterize Mead Johnson's EHC or its allergenic protein content.

Mead Johnson's 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. However, minimal information is provided regarding the method of manufacture. The source and composition of the starting material are not specified. The source, class, and activity of digestive enzymes used are not given, nor are the criteria and methods used for post-digestion processing of the ingredient.

Mead Johnson also fails to provide detailed specifications for the composition of the ingredient. Although the notification characterizes EHC by molecular weight and fragment size distributions, sufficient information is not provided on the methods used to make these determinations (including the limit of detection or quantitation), on batch-to-batch variation, or on the acceptable upper limits of the size and molecular weight distributions. Without this information, it is not possible for FDA to confirm Mead Johnson's statement that EHC contains no peptides greater than 1500 Daltons or interpret the significance of the "trace" amounts of larger peptides mentioned in the notification. More detailed specifications would be of particular interest given discrepancies in peptide distributions among the profiles provided in the notification and those provided in two included references describing EHC, as well as independent reports of lot-to-lot variability (Hoffman and Sampson, 1997) and the presence of peptides larger than 6000 Daltons in Mead Johnson EHC formulas (Mäkinen-Kiljunen et al., 1993).

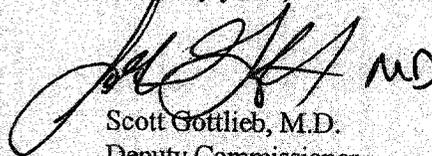
Demonstration of extensive casein digestion is not, by itself, sufficient to establish that EHC does not contain allergenic protein. As proteins are digested, important structural epitopes may be disrupted resulting in fewer immunogenic proteins. Extremely small peptides are generally not considered immunogenic. However, Mead Johnson did not provide any evidence to establish the absence of immunogenicity of somewhat larger peptides, particularly those of ten amino acids (about 1000 Daltons) or more. Peptides of this size appear to be present in Mead Johnson's EHC. There are very limited specific data in the literature available to assess the immunogenicity of such hydrolyzed peptide fragments, but there is some evidence that they may bind antibodies and induce allergic reactions in animal models (Mäkinen-Kiljunen et al., 1993).

The ELISA described in the notification appears to be intended to establish a specification for casein antigenicity in the EHC ingredient. Such tests do not directly measure the protein's allergenicity in humans, especially when primary antibodies from another species (in this case, rabbit) are used, but they can be very sensitive assays for the detection and measurement of protein. However, the method described is comparative and relies upon a reference sample. No information is provided on the sensitivity of the method or the casein content of the original sample and it is therefore not possible to determine the maximal level of casein that might be present in a batch of EHC screened by this ELISA. The information in references included in the notification is consistent with the presence of approximately one microgram of casein per gram of total protein in Mead Johnson's EHC (assuming that identical ingredients are being described). Other studies not included in the notification have shown low but detectable levels of casein in a Mead Johnson EHC formula (Sampson et al., 1991; Hoffman and Sampson, 1997). The notification does not address these studies. In addition, the ELISA method described is casein-specific and does not detect other allergenic milk proteins. This is particularly significant given the lack of information about the source material for EHC and because intact p-lactoglobulin, another allergenic milk protein (derived from whey), has been detected in Mead Johnson EHC formulas (Ma'kinen-Kiljunen et al., 1993; Rosendal and Barkholt, 2000). None of this evidence was addressed by the notification.

Conclusion

In FALN 001, Mead Johnson notifies FDA of its view that EHC does not contain allergenic protein. In FDA's view, FALN 001 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). FALN 001 neither provides sufficient scientific evidence to determine that EHC does not contain allergenic protein, nor does FALN 001 otherwise meet the requirements of section 403(w)(7). FDA therefore objects to FALN 001.

Sincerely yours,



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

References

- Bock SA. (1989) Probable allergic reaction to casein hydrolysate formula. *JACI*; 84(2):272.
- Dean TP, Adler BR, Ruge F, Warner JO. (1993) *In vitro* allergenicity of cows' milk substitutes. *Clinical and Experimental Allergy*; 23(3):205-210.
- Docena G, Rozenfeld P, Fernandez R, Fossati CA. (2002) Evaluation of the residual antigenicity and allergenicity of cow's milk substitutes by *in vitro* tests. *Allergy*; 57 (2):83-91.
- Hill DJ, Cameron DJ, Francis DE, Gonzalez-Andaya AM, Hoskings CS. (1995) Challenge confirmation of late-onset reactions to extensively hydrolyzed formulas in infants with multiple food protein intolerance. *J Allergy Clin Immunol*; 96 (3):386-94.
- Hoffman KM, Sampson HA. (1997) Serum specific-IgE antibodies to peptides detected in a casein hydrolysate formula. *Pediatr Allergy Immunol*; 8 (4):185-9.
- Kimber I, Dearman RJ, Penninks AH, Knippels LM, Buchanan RB, Hammerberg B, Jackson HA, Helm RM. (2003) Assessment of protein allergenicity on the basis of immune reactivity: animal models. *Environ Health Perspect.*; Jun;111(8):1125-30.
- Lifschitz CH, Hawkins HK, Guerra C, Byrd N. (1988) Anaphylactic shock due to cow's milk protein hypersensitivity in a breast-fed infant. *J Pediatr Gastroenterol Nutr*; 7 (1):141-4.
- Mäkinen-Kiljunen S, Sorva R. (1993) Bovine β -lactoglobulin levels in hydrolysed protein formulas for infant feeding. *Clin Exp Allergy* 1993; 23 (4):287-91.
- Rosendal A, Barkholt V. (2000) Detection of potentially allergenic material in 12 hydrolyzed milk formulas. *J Dairy Sci*; 83 (10):2200-10.
- Saylor JD, Bahna SL. (1991) Anaphylaxis to casein hydrolysate formula. *J Pediatr*; 118 (1):71-4.
- Sampson HA, Bernhisel-Broadbent J, Yang E, Scanlon SM. (1991) Safety of casein hydrolysate formula in children with cow milk allergy. *J Pediatr*; 118 (4 (Pt 1)):520-5.
- Schwartz RH. (1992) Allergy, intolerance, and other adverse reactions to foods. *Pediatr Ann*; 21 (10):654-5, 60-2, 65-74.