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September 29, 2005

CONFIDENTIAL and PROPRIETARY

Barbara O. Schneeman, Ph.D.
Office of Nutritional Products, Labeling, and Dietary Supplements (HFS-800)
Center for Food Safety and Applied Nutrition
Food and Drug Administration
5100 Paint Branch Parkway
College Park, MD 20740

RE: Allergen labeling exemption for Mead Johnson's *Extensively Hydrolyzed Casein*

Dear Dr. Schneeman:

Pursuant to Section 403(w)(7)(A)(i) of the Federal Food, Drug and Cosmetic Act ("the Act"), Mead Johnson & Company ("MJ" or "Mead Johnson") submits the attached notification requesting an exemption from the labeling requirements of subsection 403(w)(1) set forth by the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA) for MJ's Extensively Hydrolyzed Casein (EHC).

Mead Johnson's EHC is derived from milk, but does not contain the allergenic protein, as demonstrated by the scientific evidence included in this notification.

MJ's extensively hydrolyzed casein is a source of protein for hypoallergenic products (Nutramigen[®] LIPIL[®], Pregestimil[®] (b)(4) (b)(4) and 3232A. Those products are prescribed or recommended by physicians in the dietary management of documented or suspicion of cow's milk allergy and identifying the source of the EHC on the product labels would not serve the intent of FALCPA.

This letter and the information contained herein constitute proprietary information that is protected by law from disclosure. Mead Johnson & Company believes disclosure of this



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information would aid our competitors and, consequently, we have not revealed it to anyone except upon a need-to-know basis and having first obtained written commitments to hold the information in confidence.

Should you have any questions related to this submission, please contact me at 812-429-5714 or matias.diez@bms.com.

Sincerely,

A handwritten signature in cursive script that reads "Matias Diez".

Matias Diez
Manager, Regulatory Affairs
Mead Johnson & Company

CC: Benson Silverman, MD
Staff Director, Infant Formula and Medical Food Staff (HFS-850)
Office of Nutritional Products, Labeling, and Dietary Supplements
Center for Food Safety and Applied Nutrition
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SUMMARY

The Food Allergen Labeling and Consumer Protection Act (FALCPA) requires all food manufacturers to identify the presence of any of the eight major food allergens in their list of ingredients. It was enacted to better inform consumers, allowing them to make informed choices and to protect public health. Under the act, the common or usual name of the ingredient must include the food source from which the major food allergen is derived. This act was designed to make it easier for consumers to identify and avoid foods containing allergens they are allergic to. Avoiding the consumption of those food products is expected to reduce the number of reactions caused by food.

The purpose of this notification is to provide scientific evidence that Mead Johnson & Company's Extensively Hydrolyzed Casein (EHC) does not contain the allergenic protein found in the food source from which it is derived (milk) and to demonstrate that including the name of the allergen will not serve the intent of the act, but indeed create confusion and pose a risk to public health.

RATIONALE FOR EXEMPTION

As described in the Summary, the intent of the Food Allergen Labeling and Protection Act (FALCPA) is to inform consumers who are known to be allergic to a major allergen that a specific food product contains the allergen and they should avoid such food product. While consumers that are allergic to a major allergen have to restrict their dietary choices, it is important that they are not unnecessarily alarmed by the label nor further restrict their dietary options when unnecessary. Under the provision of FALCPA, any person may petition for a labeling exemption when the food ingredient does not cause an allergic response that poses a risk to human health or may file a notification for a labeling exemption, which must include scientific evidence that the food ingredient does not contain allergenic protein.

Mead Johnson's EHC, as derived by the method specified in the Manufacturing section of this notification, does not contain allergenic milk protein. All batches of the ingredient are tested according to the internal methodology (described later in the Testing section) to verify the absence of the allergenic protein. Additionally, Mead Johnson's EHC has been successfully used for over 60 years in products indicated for the dietary management of cow's milk protein allergy, becoming the standard for that indication and the reference for testing new products for hypoallergenicity. Furthermore, the ingredient subject of this notification and its suitability for individuals with cow's milk allergy has been thoroughly addressed in the following submissions: Nutramigen (April 7, 1989), Nutramigen LIPIL (April 16, 2003) submission number(s) BX0925, Pregestimil (February 10, 1986), (b)(4) and (b)(4) and 3232A – May 16, 1986.

Pursuant to Section 403(w)(7)(A)(i) of the Federal Food, Drug and Cosmetic Act ("the Act"), Mead Johnson & Company submits this notification for an exemption from the labeling requirements of subsection 403(w)(1), set forth by the Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA), for Mead Johnson's EHC.

It is Mead Johnson's preclusion that identifying the EHC in the ingredient panel as being derived from milk does not serve the intent of FALCPA, will only cause confusion, and will be a barrier to the proper utilization of formulas which contain the ingredient. Physicians recommend these formulas in cases of suspected or documented cow's milk allergy; often they are the sole source of nutrition for these infants. Identifying the EHC as being derived from milk not only is without purpose, but can create confusion for the consumer. Following a physician's recommendation, the consumer will encounter a product that is labeled as containing milk. This label may motivate the consumer to avoid the product for characterizing it as having the allergenic food they should avoid, or cause it to be perceived interchangeable with a formula with partially hydrolyzed milk or intact milk protein, which are not suitable for the dietary management of cow's milk allergy. Those situations can present a risk to human health, which contradicts the intent of FALCPA.

Based on the provision that allows for a labeling exemption, the fact that the products containing the ingredient have been successfully used in the dietary management of cow's milk allergy and the potential confusion and risk to human health caused by the identification of the ingredient as being derived from milk, Mead Johnson & Company is submitting this notification for an exemption from the allergen labeling requirements for the EHC used in the following products:

- Nutramigen LIPIL
- Pregestimil ^{(b) (4)}
- 3232A

HISTORY OF USE OF THE INGREDIENT

The EHC has been successfully used in Mead Johnson formulas for over 60 years. Nutramigen was introduced in 1942, Pregestimil in 1971, and 3232A in 1978. Since their introduction, a substantial number of references to the EHC used in these products have appeared in scientific literature.

Those references add to the evidence that the EHC does not contain the allergenic protein and is suitable for individuals with allergy to cow's milk protein. Mead Johnson formulas containing the EHC are safe and support adequate growth of infants^[1]. There are numerous clinical studies that demonstrate the nutritional adequacy and appropriateness of formulas containing the EHC^[2, 3, 4, 5, 6, 7].

EHC formulas are broadly recognized as the standard of care for infants with cow's milk allergy^[8, 9] and multiple food allergies^[10] because of the absence of cow's milk allergenic protein^[3, 4]. The hypoallergenicity of Nutramigen has been further demonstrated in animal (guinea pig) sensitization studies and in multiple human clinical studies^[1, 2, 3, 11-15].

Several authors studied the potential for allergenicity in formulas containing EHC, either by evaluating the clinical allergic reaction to the product^[11], measuring product reactivity with specific antibodies^[16], or through the measurement of antibody production in individuals exposed to the EHC^[2].

Furthermore, Nutramigen has long been recognized as the product to be used in a control group in studies that require a diet that is not expected to generate antibodies ^[17], or in studies requiring a control group with no allergic response ^[9, 12, 18] including studies evaluating the hypoallergenicity of new formulas ^[19].

The EHC, initially developed and sold for parenteral use, has a long history of safe use for parenteral and enteral feedings ^[6]. Nutramigen LIPIL, Pregestimil, ^{(b) (4)} and 3232A use the EHC as the protein source and have been successfully administered to infants with conditions that are effectively managed by feeding a formula containing EHC. These formulas have historically been, and continue to be, formulas pediatricians select when more conventional formula alternatives fail to provide tolerated nutritional support for these infants, in particular those infants who are allergic to intact cow's milk proteins ^[1, 3-9, 20-25, 26]. The clinical usefulness of Nutramigen LIPIL, Pregestimil, ^{(b) (4)} and 3232A is supported by authoritative textbook references and journal articles on the use of these products or their ingredients in the dietary management of infants with various medical conditions, including food allergy ^[2, 3, 6, 7, 9-12, 17, 18, 20-29].

Serologic and dermatologic response studies in healthy infants and children have shown that feeding Nutramigen and Pregestimil results in lower immunological responses to proteins derived from cow's milk and soy ^[2, 11, 16]. Well-controlled studies have also shown that the use of EHC formulas have a preventive effect on the development of cow's milk protein allergy/intolerance in infants at high risk of allergy ^[9, 10].

Numerous clinical research studies also promote the use of EHC formulas in children with symptoms of allergy [3, 4, 6, 9, 10, 21, 22]. Both double-blind placebo-controlled and single-blind studies provide evidence that most infants and children with cow's milk hypersensitivity are able to tolerate EHC formulas without adverse reactions [4, 10, 12, 19, 28, 29]. Furthermore, multiple studies have demonstrated that children with colic and enterocolitis caused by allergy to cow's milk or soy protein respond to Nutramigen feeding with improvement or resolution of symptoms [3, 10, 28, 29].

PRODUCT SUMMARIES

Mead Johnson produces Nutramigen LIPIL, Pregestimil, (b)(4) and 3232A hypoallergenic infant formulas which contain the EHC as the protein source – supplemented with the appropriate balance of three amino acids (L-cystine, L-tyrosine, and L-tryptophan). The protein source provides a high percentage of free amino acids and small peptides. Mead Johnson's EHC has a molecular weight profile (b)(4)

(b)(4)

Nutramigen LIPIL

Nutramigen has been in use since 1942 for parenteral and enteral feedings for infants with conditions such as protein allergy/ sensitivity/ intolerance to cow's milk protein or food allergies, carbohydrate intolerance, diarrhea, colic, and other intolerances that are effectively managed by feeding a lactose and sucrose free formula that contains EHC. Nutramigen LIPIL is considered a hypoallergenic formula as it avoids the risk of protein sensitization in allergy-prone infants and is a useful dietary management tool for infants and children with protein allergy / sensitivity including:

- Allergy, including severe or multiple food allergy
- Sensitivity or intolerance to intact cow's milk protein or other foods
- Carbohydrate intolerance ^[26, 27, 30] such as:
 - Galactosemia
 - Lactose intolerance
 - Sucrose intolerance

Nutramigen LIPIL provides protein in the form of non-antigenic amino acids and peptides, and therefore is effective in eliminating symptoms^[3, 6, 8, 9, 10, 12, 18, 23, 27, 28, 29] due to protein allergy/ sensitivity/ intolerance such as:

- Vomiting, diarrhea, excessive spitting up
- Rash, eczema, urticaria, atopic dermatitis, andioedema, chronic rhinitis
- Failure to thrive
- Asthma
- Irritability, fussiness, sleeplessness
- Excessive crying (colic)

Other benefits of Nutramigen LIPIL include:

- Sensitive G.I. tract recovery due to avoidance of further large-molecule trauma to the mucosal membranes^[18]
- A hypoallergenic formula for infants who are sensitive to intact protein found in milk-based and soy-based formulas
- Avoidance of the risk of protein sensitive enteropathy and its complications such as chronic diarrhea^[22]
- A nutritional maintenance during test or elimination diets^[3, 6, 9, 10, 12]
- A milk substitute in the diet of children with cases of severe and multiple food allergies or intolerances^[16]
- Nutramigen LIPIL provides complete nutrition, comparable to milk-based or soy-based formulas.

- Nutramigen LIPIL allows successful introduction of a nutritionally complete formula sooner after G.I. insult than possible with cow's milk or soy formulas^[18]
- Nutramigen LIPIL supports growth and bone mineralization comparable to breast-milk and Enfamil[®] with Iron

Pregestimil ^{(b) (4)}

Pregestimil was first marketed in 1971 and has been used in the feeding of infants with conditions that are effectively managed by a formula containing EHC. Pregelstimil has historically been, and continues to be, the formula pediatricians select when more conventional formula alternatives fail to provide nutritional support for infants. Pregelstimil ^{(b) (4)}

^{(b) (4)} may be recommended to address conditions such as:

- Allergy, including severe or multiple food allergies
- Sensitivity or intolerance to intact cow's milk protein or other foods
- Intolerance to lactose, galactose, or sucrose^[26, 27, 30]
- Malabsorption^[26]
 - Fat malabsorption problems associated with conditions such as cystic fibrosis, biliary atresia, celiac disease, ileectomy, severe or intractable diarrhea
 - Protein-calorie malabsorption
 - Short bowel syndrome
- Carbohydrate intolerance^[26, 30]
 - Disaccharidase deficiency
 - Lactose intolerance
 - Sucrose intolerance

Other benefits of Pregestimil ^{(b) (4)} include:

- Designed for infants with gastrointestinal problems^[27]
- Designed to provide a sole source of nutrition for infants 4-6 months, and to provide a major source of nutrition through 12 months, Pregestimil can be used as a milk substitute in the diet of children who have chronic malabsorption disorders
- A nutritional maintenance during test or elimination diets^[3, 6, 9, 10, 12]
- A hypoallergenic formula for infants who are sensitive to intact protein found in milk-based and soy-based formulas^[3]
- Pregestimil allows successful introduction of a nutritionally complete formula sooner after G.I. insult than possible with cow's milk or soy formulas^[3, 27]
- Pregestimil supports growth and bone mineralization comparable to breast-milk and Enfamil with Iron

3232A

3232A is a hypoallergenic protein hydrolysate formula base for use with added carbohydrate for infants with unusual medical or dietary problems introduced in 1978. It is a Mono- and Disaccharide-Free Diet Powder typically used for children with carbohydrate metabolism disorders such as:

- Disaccharidase deficiencies^[25, 26]
 - Lactase
 - Sucrase

- Maltase
- Hereditary Fructose Intolerance

3232A can alleviate symptoms^[25] such as:

- Vomiting
- Diarrhea
- Jaundice
- Convulsions
- Hypoglycemia
- Intractable diarrhea
- Carbohydrate malabsorption

Other benefits of 3232A include:

- Adjustment of added carbohydrate according to a patient's tolerance^[26]
- Frequently used in place of Pregestimil when glucose and glucose polymers are not tolerated^[25]

MANUFACTURING

(b)(4)
(b)(4)



Chart 1 – Protein Hyrdolysis Process

(b)(4)
(S)(4)



TESTING

Use of biochemical methods are a potent tool of allergen identification and quantification. Exposure of the food allergen induces an allergenic response primarily mediated by the immunoglobulin E (IgE) class antibodies. In a laboratory procedure like Enzyme Linked Immuno-Sorbent Assay (ELISA), these antibodies can be used as a reporter of the allergenicity induced by the particular food allergen.

After production, as described in the previous section, all batches of EHC base for Mead Johnson's Nutramigen LIPIL, Pregestimil, ^{(b) (4)} (b)(4) and 3232A are tested using the ELISA method to verify the absence of the allergenic protein. The analytical methodology used is attached (Appendix 2).

CONCLUSION

Mead Johnson's EHC, manufactured and tested as described in this notification, does not contain the allergenic cow's milk protein and is therefore exempt from the allergen labeling requirement of section 203(w)(1) of the Federal Food, Drug and Cosmetic Act (as amended by FALCPA). The exemption is anticipated in Section 403(w)(7)(A)(i) of the Federal Food, Drug and Cosmetic Act.

Identifying the EHC in the ingredient panel as being derived from milk does not serve the intent of FALCPA since the formulas containing the ingredient are recommended by physicians in cases of cow's milk allergy.

FALCPA was enacted to inform consumers about the foods that contain the allergen they should avoid, as a means to protect public health. In this case, identifying the ingredient as being derived from milk may incite the consumer to characterize the product as having the allergenic food they should avoid, further delaying the initiation of use pursuant of clarification. It may also cause the product to be perceived equivalent to a formula with partially hydrolyzed milk, which is not suitable for the dietary management of cow's milk allergy. Such situations can present a risk to public health, which contradicts the intent of FALCPA.

This notification complies with the requirements of Section 403(w)(7)(A)(i) of the Federal Food, Drug and Cosmetic Act and with the intent of the Food Labeling and Consumer Protection Act – to protect public health.

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Mead Johnson Casein Hydrolysate Peptide Profile

(b)(4)

Mead Johnson Casein Hydrolysate Molecular Weight Profile

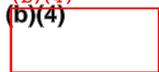
(b)(4)

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Method Description: General Method for the Determination of Antigenicity in Protein Hydrolysates

(b)(4)



(b)(4)



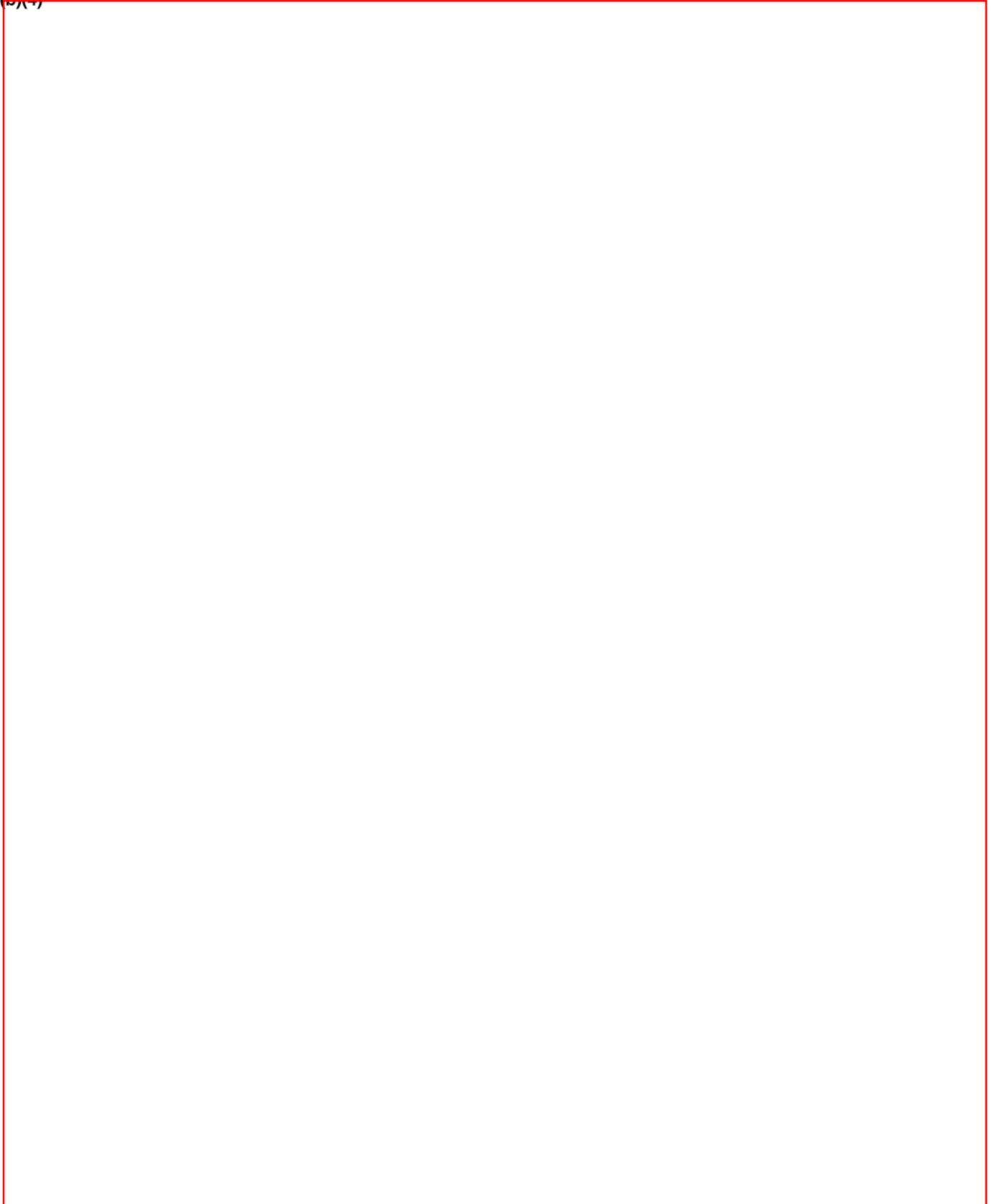
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Method Description: General Method for the Determination of Antigenicity in Protein Hydrolysates

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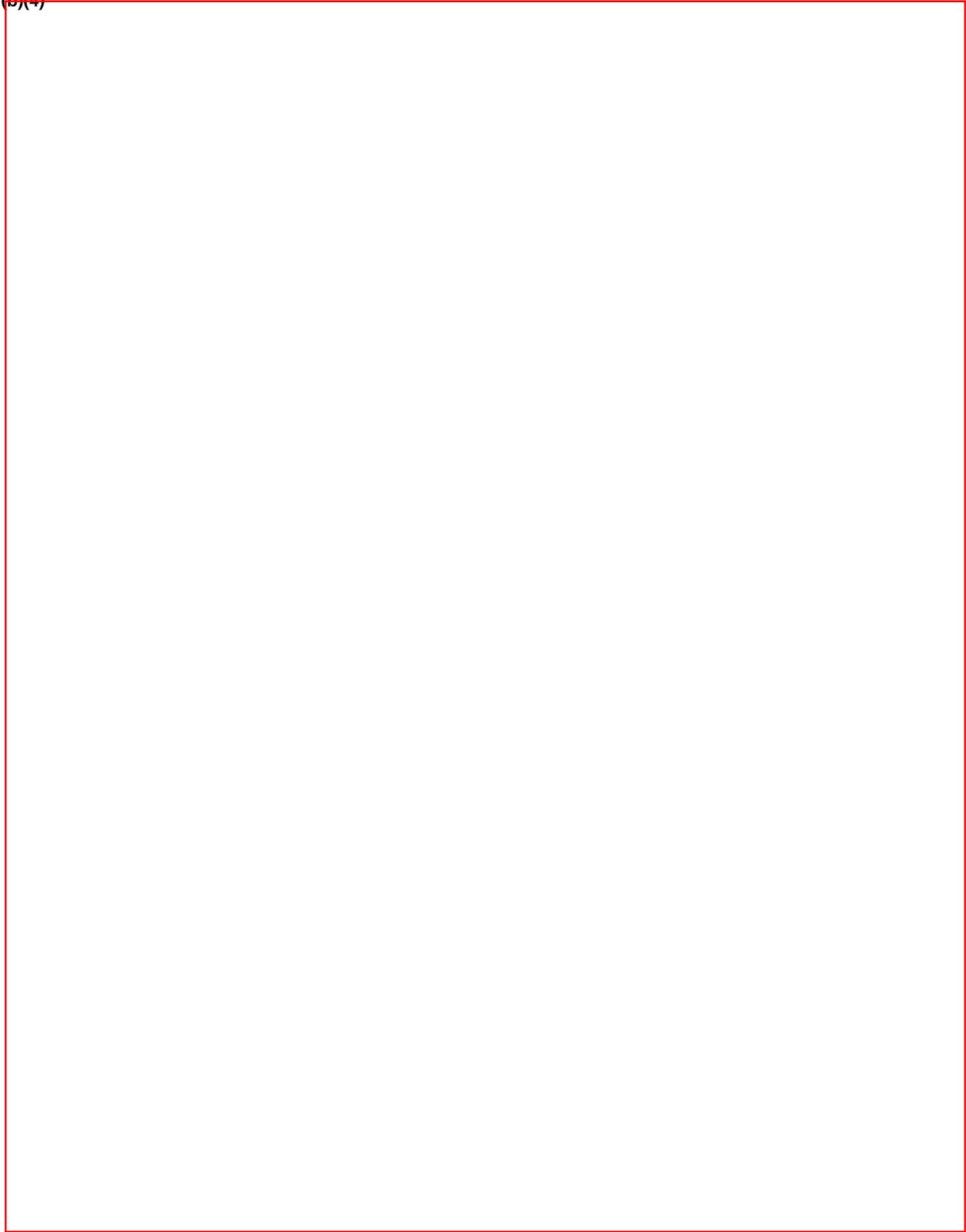
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Method Description: General Method for the Determination of Antigenicity in Protein Hydrolysates

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Method Description: General Method for the Determination of Antigenicity in Protein Hydrolysates

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