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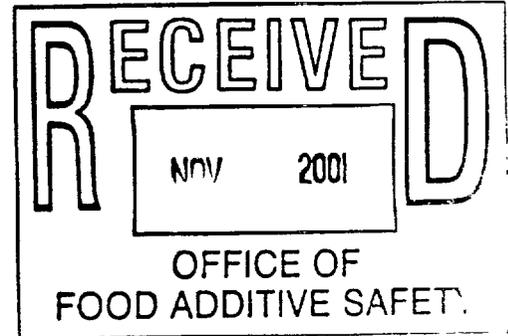
ENZYME TECHNICAL ASSOCIATION

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November 8, 2001

Office of Premarket Approval
Center for Food Safety and Applied Nutrition
Food and Drug Administration
200 C Street SW
Washington, DC 20204



RE: GRAS Notification – Exemption Claim for Ten Microbially-Derived Enzyme Preparations that are the Subject of a GRAS Affirmation Petition, GRASP 3G0016

Dear Sir or Madam:

Pursuant to proposed 21C.F.R. §§ 170.36(c)(1), 170.36(g)(2), and the Food and Drug Administration ("FDA") preamble discussion concerning the submission of a Generally Recognized As Safe ("GRAS") notification based on a previously filed GRAS affirmation petition, 62 Fed. Reg. 18938, 18953-18954 (April 17, 1997), the Enzyme Technical Association is hereby providing FDA with notice that it has determined, based on history of use, that ten microbially-derived enzyme preparations – *Aspergillus niger* (carbohydrase, catalase, glucose oxidase, pectinase, protease), *Aspergillus oryzae* (carbohydrase, protease), *Kluyveromyces marxianus* (lactase), *Rhizopus oryzae* (carbohydrase), and *Saccharomyces cerevisiae* (invertase) – as direct human food ingredients, are GRAS and therefore are exempt from statutory premarket approval requirements. These ten enzymes are also the subjects of a GRAS Affirmation Petition 3G0016 submitted by the Ad Hoc Enzyme Technical Committee (now known as the Enzyme Technical Association ("ETA")) to the FDA.

The following information is provided in accordance with the proposed regulation.

Proposed § 170.36(g)(2)(i): Name and address of the notifier.

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1800 Massachusetts Avenue, N.W.
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Proposed § 170.36(g)(2)(ii): The applicable GRAS affirmation petition number.

A GRAS Affirmation Petition for animal-derived, plant-derived, and microbially-derived enzyme preparations was originally submitted by the Ad Hoc Enzyme Technical Committee (now known as ETA) and assigned a petition number, GRASP 3G0016. The FDA filed GRASP 3G0016 on April 12, 1973 (38 Fed. Reg. 9256). The petition was amended on June 12, 1973 (38 Fed. Reg. 15471), August 29, 1984 (49 Fed. Reg. 34305), and June 23, 1987 (52 Fed. Reg. 23607) to include other plant-derived and microbially-derived enzyme preparations. This notification addresses only the ten microbial enzyme preparations named above for which FDA action is pending.

Proposed § 170.36(g)(2)(iii): The common or usual name of the substance (i.e., the notified substance).

Listed below are the common or usual names for the substances for the ten microbial enzyme preparations for which the GRAS affirmation petition was submitted and this notification is made.

NAME OF ENZYME PREPARATION	MICROBIAL SOURCE
Carbohydrase	<i>Aspergillus niger</i>
Carbohydrase	<i>Aspergillus oryzae</i>
Carbohydrase	<i>Rhizopus oryzae</i>
Catalase	<i>Aspergillus niger</i>
Glucose Oxidase	<i>Aspergillus niger</i>
Invertase	<i>Saccharomyces cerevisiae</i>
Lactase	<i>Kluyveromyces marxianus</i>
Pectinase	<i>Aspergillus niger</i>
Protease	<i>Aspergillus niger</i>
Protease	<i>Aspergillus oryzae</i>

Proposed § 170.36(g)(2)(iv): Applicable conditions of use.

As discussed in greater detail in GRASP 3G0016 as amended, the ten microbial enzyme preparations are direct human food ingredients. The uses of the enzyme preparations are for multiple technical effects:

The enzyme preparations are GRAS for use in food at levels not to exceed Good Manufacturing Practices ("GMPs").

The data and information to support the above uses are contained in GRASP 3G0016, as amended.

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Proposed § 170.36(g)(2)(v): Basis for GRAS determination.

The basis for this GRAS determination is through experience based on common use in food.

Proposed § 170.36(g)(2)(vi): Availability of information.

The complete record that supports the GRAS determination has been submitted to the agency in the above referenced GRASP 3G0016, as amended. The complete file is at FDA.

Sincerely,

Jack Harris, Chair
Enzyme Technical Association

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SUBMISSION END

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November 20, 2002

Dr. Robert Post, Director
Labeling and Consumer Protection Staff
Office of Policy, Program Development and Evaluation
Food Safety and Inspection Service
300 12th Street, SW
Room 602
Washington, DC 20250-3700

**RE: FDA GRAS Notice GRN 000089 – Protease Enzyme From *A. niger*
For Meat Tenderizing**

Dear Dr. Post:

On November 16, 2001, the Enzyme Technical Association (“ETA”) submitted a notification to the Food and Drug Administration (“FDA”) of ETA’s determination that carbohydrase, pectinase, glucose oxidase, catalase, and protease enzyme preparations derived from *Aspergillus niger* are generally recognized as safe (“GRAS”). See GRAS notice GRN 000089. FDA’s April 3, 2002 letter responding to ETA’s notification stated that the agency had “no questions at this time regarding ETA’s conclusion that carbohydrase, pectinase, protease, glucose oxidase, and catalase enzyme preparations from *Aspergillus niger* are GRAS under the intended conditions of use” (copy enclosed). However, the response goes on to state, at page 4, that, because the protease enzyme preparation could be used to tenderize meat, FDA consulted with the Labeling and Consumer Protection Staff of the USDA’s Food Safety and Inspection Service (“FSIS”). The letter further suggests that FSIS has determined that ETA has not provided data to support the “suitability” of the protease enzyme preparation from *A. niger* in meat products. As explained below, this observation, while possibly technically correct, makes no sense in light of the fact that protease enzyme preparations derived from other *Aspergillus* species have already been approved by USDA for use as meat/poultry tenderizers. See 9 C.F.R. § 424.21(c).

USDA has specifically approved the use of “proteolytic enzymes” from “*Aspergillus oryzae*” and “*Aspergillus flavus oryzae* group” for use in tenderizing meat and poultry. See id. As you may know, “protease” is within the category of enzymes that are sometimes referred to as “proteolytic.” In fact, USDA’s

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Dr. Robert Post
November 20, 2002
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approach of referring to "proteolytic enzymes" in general makes scientific sense because all such enzymes, including proteases, perform the same function, namely the breakdown of protein. Therefore, from a "suitability" perspective, it is the technical function of the enzyme (i.e., the breakdown of protein), rather than the particular source organism, that is of the greatest concern. With respect to protease, there is no significant difference in technical function between the enzyme preparations derived from different species within the *Aspergillus* genus (e.g., *A. oryzae* versus *A. niger*). All of the proteases breakdown protein – that is why they are called "protease." Thus, any remaining concerns over the specific species of *Aspergillus* from which a protease is derived would be limited to safety issues, all of which have been properly and completely addressed in FDA's response to ETA's GRAS notification.

Therefore, we believe there is more than sufficient evidence contained in USDA's regulations and ETA's GRAS notification to support the "suitability" of protease enzyme preparations from *A. niger* in meat and poultry. It is our understanding that USDA does not intend to update its regulations with new substances that are allowed for use in meat and/or poultry, relying instead on FDA's regulations. As you know, FDA is no longer reviewing GRAS Affirmation Petitions and instead is converting such petitions to GRAS Notifications, which do not result in the publication of a regulation in the Code of Federal Regulations. Accordingly, FDA's letter responding to a GRAS Notification (which is published on FDA's website) takes on greater significance when the GRAS substance is used in meat and is not listed in USDA's regulations. It is therefore imperative that the FDA letter responding to ETA's GRAS Notification clearly indicate that the protease enzyme preparation is "suitable" for meat/poultry use. Thus, we request that USDA provide **written** confirmation to ETA that the protease enzyme preparation from *Aspergillus niger* that is the subject of FDA GRAS Notice GRN 000089 is suitable for use as a meat and poultry tenderizer.

Thank you for your assistance in this matter.

Sincerely,

Wack Harris
Chair

cc: ✓ Linda Kahl, US FDA CFSAN, Office of Food Additive Safety

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October 3, 2003

Laura M. Tarantino, Ph.D.
Acting Director
Office of Food Additive Safety, HFS-200
Center for Food Safety & Applied Nutrition
US Food and Drug Administration
200 C Street, S.W.
Washington, DC 20204

**RE: Request to Add a Footnote to FDA's Website for
GRAS Notice No. GRN 000089 for the use of Protease Enzyme Preparations
from *Aspergillus niger* in Meat and Poultry Products**

Dear Dr. Tarantino:

The Food and Drug Administration issued a response to GRAS Notice No. GRN 000089 on April 4, 2002 for the use of protease enzyme preparations from *Aspergillus niger*. At the conclusion of the response, the letter notes:

Because the protease enzyme preparation from *Aspergillus niger* would be used to tenderize meat, FDA consulted with the Labeling and Consumer Protection Staff of the Food Safety and Inspection Service of the United States Department of Agriculture (FSIS) during its evaluation of GRN 000089. FSIS has determined that ETA has not provided any data to support the suitability of the protease enzyme preparation from *A. niger* for use in meat and poultry products. Suitability relates to the effectiveness of an ingredient in performing the intended purpose of use and the assurance that the conditions of use will not result in an adulterated product or one that misleads consumers. FSIS concludes that ETA needs to provide data that establish that the protease enzyme preparation is being used at the lowest level necessary to achieve the intended technical effect in the specific meat and poultry products to which application is desired.

ETA believed that the USDA information contained in the letter was incorrect and informed USDA of that fact in a letter to Mr. Robert Post on November 20, 2002. Mr. Post responded to ETA's letter on November 26, 2003 (copy enclosed) noting that the paragraph appearing in

Laura M. Tarantino, Ph.D.
October 3, 2003
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FDA's response to the GRAS notification was not correct and that protease enzyme preparations from *Aspergillus niger* are covered by the proteolytic enzyme regulations. The letter stated:

Proteolytic enzymes are listed as a class of substances in Title 9 of the Code of Federal Regulations (CFR), Section 424.21(c) for use as a tenderizing agent to treat raw poultry muscle tissue of hen, cock, mature turkey, mature duck, mature goose, mature guinea, and raw meat cuts at a level not to exceed 3 percent of the weight of the untreated product. Although protease enzymes from *Aspergillus niger* are not specifically listed in 9 CFR 424.21(c), for the purpose of a suitability determination, FSIS normally regulates the use of specific ingredients, e.g., proteolytic enzymes, not the source from which they are obtained. In this case, because FDA has no questions regarding Enzyme Technical Association's (ETA) conclusion that proteolytic enzymes obtained from *Aspergillus niger* are GRAS, FSIS would have no objection to their use in meat and dairy products.

After ETA received the letter from USDA, I discussed in April the concept of a revision of FDA's response letter with a member of the Office of Premarket Approval (OPA) and was told that FDA would not revise the letter to correct errors. While ETA recognizes that FDA will not revise the letter, we are requesting that a footnote be added outside the letter that states:

Subsequent USDA correspondence acknowledged that proteolytic enzyme preparations from *Aspergillus niger* would be covered within Title 9 of the Code of Federal Regulations (CFR), Section 424.21(c) if the FDA did not question the GRAS notification for enzyme. Specifically, proteolytic enzymes are listed for use as a tenderizing agent to treat raw poultry muscle tissue of hen, cock, mature turkey, mature duck, mature goose, mature guinea, and raw meat cuts at a level not to exceed 3 percent of the weight of the untreated product.

Such a footnote would correct a document that is clearly wrong through no error on the part of FDA or ETA. In my conversation with the FDA contact, it was suggested that we ask USDA to post their letter on USDA's Web site. That remedy, in our view, does not address the basic concern, which is that the USDA's information contained in the FDA letter is incorrect. A person accessing FDA's Web site should be informed as to USDA's regulation and not be misled by the error as reflected in the letter.

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Laura M. Tarantino, Ph.D.
October 3, 2003
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Your consideration of ETA's request is most appreciated.

Sincerely,

Gary L. Yingling
Secretary and General Counsel

Cc: ✓ Dr. Linda Kahl, FDA CFSAN
Dr. Robert Post, USDA FSIS

Enclosure(s)

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United States
Department of
Agriculture

Food Safety
and Inspection
Service

Office of Policy and
Program Development

Washington, D.C.
20250/3700

Mr. Jack Harris
Enzyme Technical Association
1800 Massachusetts Avenue, NW 2nd Floor
Washington, DC 20036-1800

NOV 26 2002

Dear Mr. Harris:

I am responding to your letters of November 20, 2002, regarding the Food Safety and Inspection Service's (FSIS) response to GRAS Notice No. GRN 000089 for the proposed use of protease enzyme preparations from *Aspergillus niger* in the production of meat and poultry products.

The Food Safety and Inspection Service (FSIS) is responsible for determining the efficacy and suitability of food ingredients and additives in meat and poultry products as well as prescribing safe conditions of use. Suitability relates to the effectiveness of an additive at the lowest level necessary to achieve the intended technical effect. As a result, FSIS expects GRAS notifications to describe the conditions of use (e.g., the species of livestock, and/or kind of poultry that are to be treated, the amount of the substance that will be applied, etc.), including the conditions of use for previously approved substances because the conditions of use may differ from what is currently approved. We are not aware of any information presented in the subject notification which addressed the criteria listed above. Consequently, at the time of review, FSIS determined that the subject GRAS notification was incomplete and that FSIS needed additional information on the specific conditions of use.

Proteolytic enzymes are listed as a class of substances in Title 9 of the Code of Federal Regulations (CFR), Section 424.21(c) for use as a tenderizing agent to treat raw poultry muscle tissue of hen, cock, mature turkey, mature duck, mature goose, mature guinea, and raw meat cuts at a level not to exceed 3 percent of the weight of the untreated product. Although protease enzymes from *Aspergillus niger* are not specifically listed in 9 CFR 424.21(c), for the purpose of a suitability determination, FSIS normally regulates the use of specific ingredients, e.g., proteolytic enzymes, not the source from which they are obtained. In this case, because FDA has no questions regarding Enzyme Technical Association's (ETA) conclusion that proteolytic enzymes obtained from *Aspergillus niger* are GRAS, FSIS would have no objection to their use in meat and poultry products. However, similar to other proteolytic enzymes listed in 9 CFR Section 424.2(c), proteolytic enzymes obtained from *Aspergillus niger* would be limited in use to treat raw poultry muscle tissue of hen, cock, mature turkey, mature duck, mature goose, mature guinea, and raw meat cuts at a level not to exceed 3 percent of the weight of the untreated product. If ETA's proposed use deviates from these conditions specified in 9 CFR 424.21(c), FSIS would need suitability data on the proposed conditions of use to perform an acceptability determination.

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Mr. Jack Harris

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If you need any additional information, do not hesitate to contact Jeff Canavan,
Food Technologist, or myself at Area Code (202) 205-0279.

Sincerely,

Robert C. Post, Ph.D., Director
Labeling and Consumer Protection Staff

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