

GR



ORIGINAL SUBMISSION

000001

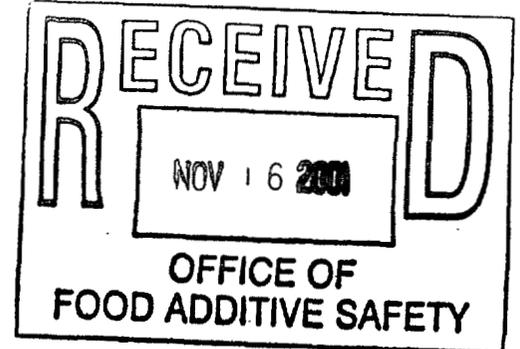


ENZYME TECHNICAL ASSOCIATION

1800 Massachusetts Avenue, NW, 2nd Floor
Washington, DC 20036-1800

Telephone (202) 778-9335
Fax (202) 778-9100
www.enzymetechnicalassoc.org

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.

Enzyme Technical Association
1800 Massachusetts Avenue, N.W.
Second Floor
Washington, DC 20036

000002

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.

000003

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

000004

SUBMISSION ENB

000005



ENZYME TECHNICAL ASSOCIATION

1800 Massachusetts Avenue, NW, 2nd Floor
Washington, DC 20036-1800

Telephone (202) 778-9335
Fax (202) 778-9100
www.enzymetechnicalassoc.org

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 000090 – Protease Enzyme From *A. oryzae*
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 and protease enzyme preparations derived from *Aspergillus oryzae* are generally recognized as safe ("GRAS"). See GRAS notice GRN 000090. FDA's April 4, 2002 letter responding to ETA's notification stated that the agency had "no questions at this time regarding ETA's conclusion that carbohydrase and protease enzyme preparations from *A. oryzae* 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. oryzae* in meat products. This observation is incorrect in light of the fact protease enzyme preparations from *A. oryzae* have already been approved by USDA for use as tenderizers in meat and poultry. See 9 C.F.R. § 424.21(c).

As you know, section 424.21(c), Title 9 of the Code of Federal Regulations contains a consolidated list of food ingredients that are approved for use in the preparation of meat and/or poultry products (provided they are used for the indicated purposes, within the stated amounts and in accordance with applicable restrictions). This list contains a specific reference to "proteolytic enzymes" from "*Aspergillus oryzae*" for the purpose of softening tissue in raw poultry and meat. 9 C.F.R. § 424.21(c). The regulation also

Dr. Robert Post
November 20, 2002
Page 2

contains a reference to "tenderizing agents," under which *A. oryzae* is listed, again for the purpose of softening tissue in raw poultry and meat. Id. The permitted amount for both "proteolytic enzymes" and "tenderizing agents" is the same. Namely, "solutions consisting of water and approved proteolytic enzyme applied or injected into raw meat or poultry tissue shall not result in a gain of more than 3 percent above the weight of the untreated product." Id.

It therefore appears that FSIS has already reviewed protease (which is a proteolytic enzyme) derived from *A. oryzae* and concluded that it is suitable for use in meat and poultry as a meat tenderizer. As such, ETA does not believe that additional data is required at this time.

We would greatly appreciate your written confirmation from USDA that FDA's statement alleging a lack of data supporting the suitability of protease enzyme preparations from *A. oryzae* is incorrect and that the enzyme is approved for use as a tenderizer in meat and poultry.

Sincerely,

Jack Harris
Chair

Enclosure(s)

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

000024
~~000026~~



ENZYME TECHNICAL ASSOCIATION

1800 Massachusetts Avenue, NW, 2nd Floor
Washington, DC 20036-1800

Telephone (202) 778-9335
Fax (202) 778-9100
www.enzymetechnicalassoc.org

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 000090 for the use of Protease Enzyme Preparations
from *Aspergillus oryzae* in Meat and Poultry Products**

Dear Dr. Tarantino:

The Food and Drug Administration issued a response to GRAS Notice No. GRN 000090 on April 4, 2002 for the use of protease enzyme preparations from *Aspergillus oryzae*. At the conclusion of the response, the letter notes:

Because the protease enzyme preparation from *Aspergillus oryzae* 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 000090. FSIS has determined that ETA has not provided any data to support the suitability of the protease enzyme preparation from *A. oryzae* 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
Page 2

FDA's response to the GRAS notification was not correct and that protease enzyme preparations from *Aspergillus oryzae* and *Aspergillus flavus oryzae* group:

are currently listed for use in Title 9 of the Code of Federal Regulations (CFR), Section 424.21(c). Specifically, they 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.

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 protease enzyme preparations from *Aspergillus oryzae* and *Aspergillus flavus oryzae* group are currently listed for use in Title 9 of the Code of Federal Regulations (CFR), Section 424.21(c). Specifically, they 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.

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)

000 026
000031

RECEIVED
3/22/03



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 000090 for the proposed use of protease enzyme preparations from *Aspergillus oryzae* in the production of meat and poultry products.

FSIS shares the responsibility of approving ingredients used in the production of meat and poultry with the Food and Drug Administration (FDA). 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 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.

However, you are correct, *Aspergillus oryzae* and *Aspergillus flavus oryzae* group are currently listed for use in Title 9 of the Code of Federal Regulations (CFR), Section 424.21(c). Specifically, they 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. If a proposed use of *Aspergillus Oryzae* differs from the conditions of use listed in 9 CFR 424.21(c), FSIS would have to review the request with supporting documentation as an acceptability determination. This process is described in the memorandum of understanding (MOU) between FDA and FSIS that can be found on our website: www.fsis.usda.gov/OPPDE/larc/.

000 027
-000032

Jack Harris
Page 2

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

000 028
~~000033~~