U. S. Food and Drug Administration
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
December 20, 2002

Agency Response Letter
GRAS Notice No. GRN 000111

Jack Harris
Enzyme Technical Association
c/o Gary L. Yingling
1800 Massachusetts Avenue, NW, Second Floor
Washington, DC 20036-1800

Re: GRAS Notice No. GRN 000111

Dear Mr. Harris:

The Food and Drug Administration (FDA) is responding to the notice, dated August 5, 2002, that you submitted in accordance with the agency's proposed regulation, proposed 21 CFR 170.36 (62 FR 18938; April 17, 1997; Substances Generally Recognized as Safe (GRAS); the GRAS proposal). FDA received the notice on August 15, 2002, filed it on August 16, 2002, and designated it as GRAS Notice No. GRN 000111.

The subject of the notice is lipase enzyme preparation from a nontoxigenic and nonpathogenic strain of *Aspergillus niger*. The notice informs FDA of the view of the Enzyme Technical Association (ETA) that the lipase enzyme preparation is GRAS, through scientific procedures, for use as an enzyme in dairy-based flavoring preparations, cheeses, liquid and dried egg white, bread, flour,bakery products not subject to a standard of identity, modified triglycerides, hydrolyzed lecithin, edible fats and oils, and modified egg yolk. The lipase enzyme preparation is used in food at minimum levels necessary to achieve the intended technical effect. This enzyme preparation is also the subject of a GRAS affirmation petition (GRP 3G0016) submitted to FDA in 1973 by the Ad Hoc Enzyme Technical Committee (now known as ETA) and amended a few times thereafter. In its notice, the ETA requested that FDA convert the filed GRAS affirmation petition GRP 3G0016 for this enzyme preparation to a GRAS notice in accordance with the agency's GRAS proposal.

Commercial enzyme preparations that are used in food processing typically contain an enzyme component, which catalyzes the chemical reaction that is responsible for its technical effect, as well as substances used as stabilizers, preservatives or diluents. Enzyme preparations may also contain constituents that derive from the source organism and constituents that derive from the manufacturing process, e.g., components of the fermentation media or the residues of processing aids. ETA's notice provides information about each of these components of the lipase enzyme preparation from *A. niger*.

In assessing the safety of the enzyme itself, ETA discusses the history of safe use of lipases in food processing. ETA cites published articles reporting the use of microbial lipases in food production since 1952. ETA describes specific lipase enzyme preparations that have been used in food, including the

following:

- Lipase from *A. niger* (i.e., the subject of ETA's notice), which FDA has included in its generally available document entitled "Partial List of Enzyme Preparations That Are Used in Foods," (available on the Internet at http://www.cfsan.fda.gov/~dms/opa enzy.html)
- Animal lipase, which FDA affirmed as GRAS for use as an enzyme to hydrolyze fatty acid glycerides (21 CFR 184.1415)
- Lipase enzyme preparation derived from *Rhizopus niveus*, which FDA affirmed as GRAS for use as an enzyme for the interesterification of fats and oils (21 CFR 184.1420)
- Esterase-lipase derived from *Mucor miehei* (now known as *Rhizomucor miehei*), which FDA approved for use as a flavor enhancer (21 CFR 173.140)
- Immobilized esterase-lipase enzyme preparation from *M. miehei*, which FDA filed as GRAS affirmation petition GRP 7G0323 in 1989 (54 FR 9565)
- Lipase enzyme preparation from *A. oryzae* carrying a gene encoding lipase from *Thermomyces lanuginosus*, which Novozymes North America, Inc. (Novozymes) determined to be GRAS for use in dough, baked goods, and the fats and oil industry (GRAS Notice No. GRN 000043)
- Lipase enzyme preparation from *A. oryzae* carrying a recombinant gene encoding lipase from *Fusarium oxysporum*, which Novozymes determined to be GRAS for use as a processing aid in the modification of fats and oils, and in baking applications (GRAS Notice No. GRN 000075)
- Lipase enzyme preparation from *A. oryzae* carrying a recombinant gene encoding a modified lipase gene from *T. lanuginosus* and a portion of the *F. oxysporum* lipase gene, which Novozymes determined to be GRAS for use as a processing aid in the modification of fats and oils (GRAS Notice No. GRN 000103).

ETA describes the catalytic activity of the lipase as hydrolyzing ester bonds in triglycerides, resulting in the formation of free fatty acids, diglycerides, and monoglycerides. The hydrolysis reaction is reversible. Therefore, the enzyme can also catalyze the synthesis of ester bonds under appropriate conditions. The systematic name of lipase is triacylglycerolacylhydrolase and the Enzyme Commission number is 3.1.1.3.

In assessing the safety of the production organism, *A. niger*, ETA cites scientific review articles in support of its view that the safety of the production organism is the prime consideration in assessing the safety of an enzyme preparation intended for use in food. ETA also cites a publication of the International Food Biotechnology Council which concludes that if the production microorganism is nontoxigenic and nonpathogenic and the manufacturing process is conducted using current Good Manufacturing Practices, the food or food ingredient produced from that microorganism is safe to consume. ETA considers *A. niger* to be nontoxigenic and nonpathogenic based on published criteria for safety assessment and a long history of safe use documented in numerous scientific publications.

ETA describes the manufacturing process for the lipase enzyme preparation, which is produced from a nontoxigenic and nonpathogenic strain of *A. niger* by pure culture fermentation. The fermentation procedure is carried out by submerged culture, solid culture, or a semi-solid culture method. The controlled process is monitored for contamination with other microorganisms and if contamination is detected, the fermentation is terminated and the batch is rejected. After fermentation, the lipase is recovered, purified and concentrated. The enzyme is formulated as either a liquid or dry product with stabilizers, diluents, and/or preservatives added to the formulated enzyme preparation. ETA states that the fermentation media and all substances added to the enzyme preparation are suitable for general use in food. The enzyme preparation meets the general and additional requirements for enzyme preparations in the monograph on enzyme preparations in the Food Chemicals Codex, 4th edition (1996).

Based on the information provided by ETA, as well as the information in GRP 3G0016 and other

information available to FDA, the agency has no questions at this time regarding ETA's conclusion that the lipase enzyme preparation from *A. niger* is GRAS under the intended conditions of use. The agency has not, however, made its own determination regarding the GRAS status of the subject use of this lipase enzyme preparation. As always, it is the continuing responsibility of each manufacturer to ensure that food ingredients that the firm markets are safe, and are otherwise in compliance with all applicable legal and regulatory requirements.

In accordance with the interim policy discussed in the GRAS proposal (62 FR 18938 at 18954), FDA has not committed any resources to review of GRP 3G0016 since the date that we received ETA's conversion request.

In accordance with proposed 21 CFR 170.36(f), a copy of the text of this letter, as well as a copy of the information in the notice that conforms to the information in proposed 21 CFR 170.36(c)(1), is available for public review and copying on the homepage of the Office of Food Additive Safety (on the Internet at http://www.cfsan.fda.gov/~lrd/foodadd.html).

Sincerely,
/s/
Alan M. Rulis, Ph.D.
Director
Office of Food Additive Safety
Center for Food Safety
and Applied Nutrition

Food Ingredients and Packaging | Summary of all GRAS Notices

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