

(b) * * *

Substances	Limitations
Octadecyl 3,5-di-tert-butyl-4-hydroxyhydrocinnamate (CAS Reg. No. 2082-79-3).	For use only * * * 12. At levels not exceeding 0.2 percent by weight of vinylidene chloride homopolymers and/or vinylidene chloride copolymers complying with applicable regulations in Parts 175, 176, 177, 179, and 181 of this chapter. The vinylidene chloride copolymers shall contain not less than 50 weight percent of total polymer units derived from vinylidene chloride.

Any person who will be adversely affected by the foregoing regulation may at any time on or before February 3, 1983, submit to the Dockets Management Branch (address above), written objections thereto and may make a written request for a public hearing on the stated objections. Each objection shall be separately numbered and each numbered objection shall specify with particularity the provision of the regulation to which objection is made. Each numbered objection on which a hearing is requested shall specifically so state; failure to request a hearing for any particular objection shall constitute a waiver of the right to a hearing on that objection. Each numbered objection for which a hearing is requested shall include a detailed description and analysis of the specific factual information intended to be presented in support of the objection in the event that a hearing is held; failure to include such a description and analysis for any particular objection shall constitute a waiver of the right to a hearing on the objection. Three copies of all documents shall be submitted and shall be identified with the docket number found in brackets in the heading of this regulation. Received objections may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Effective date. This regulation shall become effective, January 4, 1983.

(Secs. 201(s), 409, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348))

Dated: December 23, 1982.

William F. Randolph,
Acting Associate Commissioner for
Regulatory Affairs.

[FR Doc. 83-49 Filed 1-3-83; 8:45 am]

BILLING CODE 4180-01-M

21 CFR Part 184

[Docket No. 82G-0010]

Direct Food Substances Affirmed as GRAS, Mixed Carbohydrase and Protease Enzyme Product

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is affirming that mixed carbohydrase and protease enzyme product derived from *Bacillus licheniformis* is generally recognized as safe (GRAS) when used to hydrolyze starches and proteins in the production of certain foods. This action is based on an industry petition requesting such affirmation.

EFFECTIVE DATE: January 4, 1983.

FOR FURTHER INFORMATION CONTACT: Mary C. Custer, Bureau of Foods (HFF-335), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-426-9463.

SUPPLEMENTARY INFORMATION: In accordance with the procedures described in § 170.35 (21 CFR 170.35), Novo Laboratories, Inc., Danbury Rd., Wilton, CT 06897, submitted a petition (GRASP 3G0026) requesting affirmation that mixed carbohydrase and protease enzyme product derived from *Bacillus licheniformis* used as an enzyme in the production of nutritive sweeteners, beer, distilled spirits, and protein hydrolyzates is GRAS. A notice of filing of the petition was published in the Federal Register of September 12, 1973 (38 FR 25214), and interested persons were given an opportunity to review the petition and to submit comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

In response to the notice, one comment was received from the manager of microbiological research at a large firm. The comment questioned the statement made by the petitioner that *B. licheniformis* is a member of the *Bacillus subtilis* group and the petitioner's contention that all the data available to show the safety of carbohydrase and proteases prepared from *B. subtilis* are applicable to the mixture derived from *B. licheniformis*. The respondent pointed out that *B. licheniformis* had been classified as a separate and distinct species from *B. subtilis* as early as 1944 and used examples to show that the safety data for one organism do not automatically guarantee the safety of another albeit closely related, organism.

The agency concurs with the comment and concludes that the safety of mixed carbohydrase and protease enzyme product derived from *B. licheniformis* should be evaluated on the basis of scientific procedures, not on the basis of the history of use of similar enzyme preparations from *B. subtilis*, as requested by the petitioner.

Mixed carbohydrase and protease enzyme product is an enzyme preparation that includes amylases and proteases. It is obtained from the culture filtrate resulting from a pure culture fermentation of a nonpathogenic strain of the organism *B. licheniformis*. The enzyme mixture is standardized with respect to amylase or protease activity by the addition of an appropriate amount of dilute sodium chloride solution. The enzyme product, as prepared, should meet the specifications for enzymes of the Food Chemicals Codex, 3d Ed. (1981).

The applications of mixed carbohydrase and protease enzyme preparations in the food industry fall into two separate areas based upon the principal reaction that is being catalyzed by the enzymes in the mixture. The amylase portion of the mixture catalyzes the hydrolysis of starch to water soluble sugars, and the protease portion of the mixture catalyzes the hydrolysis of proteins to smaller, usually more soluble, proteins and polypeptides.

Mixed carbohydrase and protease enzyme preparations are used in the brewing and distilling industries to liquify the starch in mashes or adjuncts. These preparations may also be used to dissolve starch in cane juice to facilitate the subsequent filtration process. Likewise, the enzyme preparation can be used to recover sugars from scrap candy that contains starch as a gelling agent.

The mixed carbohydrase and protease enzyme product derived from *B. licheniformis* has been used to degrade gelled starch to water soluble sugars in the corn syrup industry since 1972. This enzyme preparation has also been used in the experimental production of protein hydrolyzates since 1971.

Published scientific literature as well as standard books on food microbiology demonstrate that *B. licheniformis* is widely recognized as a common contaminant found in many foods. None of these references report any toxicity or pathogenicity associated with the presence of this organism in food.

A search of the scientific literature reported by the petitioner disclosed no evidence that *B. licheniformis* produces disease in man. One published

pathogenicity study reported that *B. licheniformis* was not pathogenic in mice or guinea pigs.

The petition also contains unpublished pathogenicity studies, animal feeding studies, and dermal studies to support the safety of the enzyme preparation. The unpublished pathogenicity studies on the particular strain of *B. licheniformis* covered by the petition confirm that this strain of *B. licheniformis* is neither pathogenic nor toxicogenic to rats, mice, guinea pigs, and rabbits. The animal feeding studies, including LD₅₀s in both sexes of mice and rats, a 28-day study in the rat, two 90-day studies in the rat and the dog, respectively, a teratology study in the rat, and two dominant lethal studies in the male mouse and male rat, respectively, provide data that corroborate that anticipated levels of the enzyme preparation in food are safe for human consumption. The dermal studies on rabbit skin and rabbit eye mucosa showed, respectively, moderate and minimal irritation. However, the agency believes that these effects are not relevant to the safety of the enzyme preparation as a food ingredient.

The agency has evaluated all the information related to the use of mixed carbohydrase and protease enzyme product derived from *B. licheniformis* in food and has reached the following conclusions:

1. The enzyme product is not GRAS based on history of common use in food.
2. The enzyme product is GRAS based on scientific procedures. This conclusion is based on published information establishing that *B. licheniformis* is widely recognized as a harmless contaminant found in many foods. This conclusion is corroborated by unpublished animal feeding studies that confirm that food uses of the enzyme product derived from *B. licheniformis* are safe.

The agency has also concluded that it is both impractical and unnecessary to include levels of use in the GRAS affirmation regulation for mixed carbohydrase and protease enzyme product derived from *B. licheniformis*. A set of percentage-by-weight levels of use would not be meaningful because of the varying activity levels of individual enzyme preparations, and the use of this enzyme preparation in many foods is self-limiting because the addition of excessive amounts results in a degree of hydrolysis that produces products of unacceptable texture. Therefore, the agency is affirming the GRAS status of mixed carbohydrase and protease enzyme product derived from *B.*

licheniformis when it is used under current good manufacturing practice conditions of use in accordance with § 184.1(b)(1) (21 CFR 184.1(b)(1)). To make clear, however, that the affirmation of the GRAS status of this substance is based on the evaluation of limited uses, the regulation sets forth the technical effect and the food uses of this ingredient that FDA evaluated.

In the Federal Register of September 7, 1982 (47 FR 39199), FDA proposed to adopt a general policy restricting the circumstances in which it will specifically describe conditions of use in regulations affirming substances as GRAS under 21 CFR 184.1(b)(1) or 186.1(b)(1). The agency proposed to amend its regulations to indicate clearly that it will specify one or more of the current good manufacturing practice conditions of use in regulations for substances affirmed as GRAS with no limitations other than current good manufacturing practice only when the agency determines that it is appropriate to do so.

The format of the final regulation is different from that in previous GRAS affirmation regulations. FDA has modified paragraph (c) of § 184.1027 to make clear the agency's determination that GRAS affirmation is based upon current good manufacturing practice conditions of use, including both the technical effects and food categories listed. This change has no substantive effect but is made merely for clarity.

The agency has determined pursuant to 21 CFR 25.24(d)(6) (proposed December 11, 1979; 44 FR 71742) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

In accordance with Executive Order 12291, FDA has carefully analyzed the economic effects of this rule and the agency has determined that the rule is not a major rule as defined by the Order. A copy of the threshold assessment supporting this determination is on file with the Dockets Management Branch (address above).

List of Subjects in 21 CFR Part 184

Direct food ingredients, Food ingredients, Generally recognized as safe (GRAS) food ingredients.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348,

371(a))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), Part 184 is amended by adding new § 184.1027 to read as follows:

PART 184—DIRECT FOOD SUBSTANCES AFFIRMED AS GENERALLY RECOGNIZED AS SAFE

§ 184.1027 Mixed carbohydrase and protease enzyme product.

(a) Mixed carbohydrase and protease enzyme product is an enzyme preparation that includes carbohydrase and protease activity. It is obtained from the culture filtrate resulting from a pure culture fermentation of a nonpathogenic strain of *B. licheniformis*.

(b) The ingredient meets the specifications of the Food Chemicals Codex, 3d Ed. (1981), p. 107, which is incorporated by reference. Copies are available from the National Academy Press, 2101 Constitution Ave. NW., Washington, DC 20418, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC 20408.

(c) In accordance with § 184.1(b)(1), the ingredient is used in food with no limitation other than current good manufacturing practice. The affirmation of this ingredient as generally recognized as safe as a direct human food ingredient is based upon the following current good manufacturing practice conditions of use:

(1) The ingredient is used as an enzyme, as defined in § 170.3(o)(9) of this chapter, to hydrolyze proteins or carbohydrates.

(2) The ingredient is used in the following foods at levels not to exceed current good manufacturing practice: alcoholic beverages, as defined in § 170.3(n)(2) of this chapter, candy, nutritive sweeteners, and protein hydrolyzates.

Effective date. This regulation shall become effective January 4, 1983.

(Secs. 201(s), 409, 701(a), 52 Stat. 1055, 72 Stat. 1784-1788 as amended (21 U.S.C. 321(s), 348, 371(a)))

Dated: December 8, 1982.

William F. Randolph,
Acting Associate Commissioner for
Regulatory Affairs.

Note.—Incorporation by reference was approved by the Director of the Office of the Federal Register on April 1, 1982, and is on file in the Office of the Federal Register.

[FR Doc. 83-3 Filed 1-3-83; 8:45 am]

BILLING CODE 4160-1-M

21 CFR Part 522

Implantation or Injectable Dosage Form New Animal Drugs Not Subject to Certification; Trimethoprim and Sulfadiazine Sterile Suspension

AGENCY: Food and Drug Administration.
ACTION: Final rule.

SUMMARY: The Food and Drug Administration is amending the animal drug regulations to reflect approval of a new animal drug application (NADA) filed by Wellcome Animal Health Div., Burroughs Wellcome Co., providing for safe and effective use in horses of a combination antibacterial drug containing trimethoprim and sulfadiazine.

EFFECTIVE DATE: January 4, 1983.

FOR FURTHER INFORMATION CONTACT: Sandra K. Woods, Bureau of Veterinary Medicine (HFV-114), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3420.

SUPPLEMENTARY INFORMATION: Wellcome Animal Health Div., Burroughs Wellcome Co., 3030 Cornwallis Rd., Research Triangle Park, NC 27709, filed an NADA (106-965) providing for intravenous use of Tribrissen 48% Injection (a sterile suspension containing 80 milligrams (mg) of trimethoprim and 400 mg of sulfadiazine per milliliter (mL)) for treating bacterial infections in horses. The firm also holds approval for use of Tribrissen 24% Injection in dogs. Use of the injection in horses is indicated where control of bacterial infections is required during treatment of acute strangles, respiratory tract infections, acute urogenital infections, and wound infections and abscesses. The firm submitted effectiveness data that comply with the Bureau of Veterinary Medicine's combination drug guidelines. The data generated by several field investigations, and also from several general infection models, demonstrate substantial evidence of the drug's effectiveness. Therefore, the Bureau granted a waiver from the requirement of 21 CFR 514.111(a)(5)(ii) that the field investigations specifically qualify as adequate and well-controlled studies based on certain criteria designated by the section. Safety of the drug combination to horses is established. The NADA is approved, and the regulations are amended to reflect the approval.

In accordance with the freedom of information provisions of Part 20 (21 CFR Part 20) and § 514.11(e)(2)(ii) (21 CFR 514.11(e)(2)(ii)), a summary of safety and effectiveness data and information submitted to support

approval of this application may be seen in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, Md. 20857, from 9 a.m. to 4 p.m., Monday through Friday.

The Bureau of Veterinary Medicine has carefully considered the potential environmental effects of this action and has concluded that the action will not have a significant impact on the human environment and that an environmental impact statement therefore will not be prepared. The Bureau's finding of no significant impact and the evidence supporting this finding, contained in the environmental impact analyses report (pursuant to 21 CFR 25.1(f)(1)(ii)), may be seen in the Dockets Management Branch (address above).

This action is governed by the provisions of 5 U.S.C. 556 and 557 and is therefore excluded from Executive Order 12291 by section 1(a)(1) of the Order.

List of Subjects in 21 CFR Part 522

Animal drugs, Injectable.

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512(i), 82 Stat. 347 (21 U.S.C. 360b(i))) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10) and redelegated to the Bureau of Veterinary Medicine (21 CFR 5.83), § 522.2610 is revised, to read as follows:

PART 522—IMPLANTATION OR INJECTABLE DOSAGE FORM NEW ANIMAL DRUGS NOT SUBJECT TO CERTIFICATION**§ 522.2610 Trimethoprim and sulfadiazine sterile suspension.**

(a)(1) *Specifications.* Each milliliter of sterile aqueous suspension contains 240 milligrams (40 milligrams of trimethoprim and 200 milligrams of sulfadiazine).

(2) *Sponsor.* See 017220 in § 510.600(c) of this chapter.

(3) *Conditions of use—(i) Dosage.* One milliliter (40 milligrams of trimethoprim and 200 milligrams of sulfadiazine) per 20 pounds (9 kilograms) of body weight per day.

(ii) *Indications.* For dogs for treatment of acute urinary tract infections, acute bacterial complications of distemper, acute respiratory tract infections, acute alimentary tract infections, and acute septicemia due to *Streptococcus zooepidemicus*.

(iii) *Limitations.* For subcutaneous use in dogs only; administer once every 24 hours, or for severe infections, after an initial dose, administer half the normal daily dose every 12 hours; continue therapy 2 to 3 days after clinical signs of

infection have subsided; if no improvement is seen in 3 to 5 days, reevaluate diagnosis; injection may be used alone or in conjunction with oral dosing; not recommended for use for more than 14 days; a complete blood count should be done for prolonged use; Federal law restricts this drug to use by or on the order of a licensed veterinarian.

(b)(1) *Specifications.* Each milliliter of sterile aqueous suspension contains 480 milligrams (80 milligrams of trimethoprim and 400 milligrams of sulfadiazine (as the sodium salt)).

(2) *Sponsor.* See 017220 in § 510.600(c) of this chapter.

(3) *Conditions of use—(i) Dosage.* Two milliliters (160 milligrams of trimethoprim and 800 milligrams of sulfadiazine) per 100 pounds (45 kilograms) of body weight per day.

(ii) *Indications.* For horses where systemic anti-bacterial action against sensitive organisms is required during treatment of acute strangles, respiratory tract infections, acute urogenital infections, and wound infections and abscesses.

(iii) *Limitations.* For intravenous use; administer as single, daily dose for 5 to 7 days; daily dose may also be halved and given morning and evening; continue acute infection therapy 2 to 3 days after clinical signs have subsided; if no improvement of acute infections is seen in 3 to 5 days, reevaluate diagnosis; a complete blood count should be done periodically for prolonged use; not for use in horses intended for food; Federal law restricts this drug to use by or on the order of a licensed veterinarian.

Effective date. January 4, 1983.
 (Sec. 512(i), 82 Stat. 347 (21 U.S.C. 360 b(i)).)

Dated: December 21, 1982.

Lester M. Crawford,

Director, Bureau of Veterinary Medicine.

[FR Doc. 83-2 Filed 1-3-83, 8:45 am]

BILLING CODE 4150-01-M

DEPARTMENT OF LABOR**Occupational Safety and Health Administration****29 CFR Part 1990****Identification, Classification and Regulation of Potential Occupational Carcinogens; Partial Stay**

AGENCY: Occupational Safety and Health Administration (OSHA), Labor.

ACTION: Partial administrative stay.

SUMMARY: On January 5, 1982, OSHA published a combined advance notice of