

sodium polyacrylate-acrylamide resin for control of organic and mineral scale in beet sugar juice and liquor or cane sugar juice and liquor.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 409(c)(1), 72 Stat. 1786; 21 U.S.C. 348(c)(1)) and under authority delegated to the Commissioner (21 CFR 2.120), § 121.1092 is revised to read as follows:

**§ 121.1092 Acrylate-acrylamide resins.**

Acrylate-Acrylamide resins may be safely used in food under the following prescribed conditions:

(a) The additive consists of one of the following:

(1) Acrylamide-acrylic acid resin (hydrolyzed polyacrylamide) is produced by the polymerization of acrylamide with partial hydrolysis, or by copolymerization of acrylamide and acrylic acid, with the greater part of the polymer being composed of acrylamide units.

(2) Sodium polyacrylate-acrylamide resin is produced by the polymerization and subsequent hydrolysis of acrylonitrile in a sodium silicate-sodium hydroxide aqueous solution, with the greater part of the polymer being composed of acrylate units.

(b) The additive contains not more than 0.05 percent of residual monomer calculated as acrylamide.

(c) The additive is used or intended for use as follows:

(1) The additive identified in paragraph (a)(1) of this section is used as a flocculent in the clarification of beet sugar juice or cane sugar juice in an amount not to exceed 5 parts per million by weight of the juice.

(2) The additive identified in paragraph (a)(2) of this section is used to control organic and mineral scale in beet sugar juice and liquor or cane sugar juice and liquor in an amount not to exceed 2.5 parts per million by weight of the juice or liquor.

Any person who will be adversely affected by the foregoing order may at any time within 30 days after its date of publication in the FEDERAL REGISTER file with the Hearing Clerk, Department of Health, Education, and Welfare, Room 6-88, 5600 Fishers Lane, Rockville, Md. 20852, written objections thereto in quadruplicate. Objections shall show wherein the person filing will be adversely affected by the order and specify with particularity the provisions of the order deemed objectionable and the grounds for the objections. If a hearing is requested, the objections must state the issues for the hearing. A hearing will be granted if the objections are supported by grounds legally sufficient to justify the relief sought. Objections may be accompanied by a memorandum or brief in support thereof. Received objections may be seen in the above office during working hours, Monday through Friday.

**Effective date.** This order shall become effective on its date of publication in the FEDERAL REGISTER (1-11-72).

(Sec. 409(c)(1), 72 Stat. 1786; 21 U.S.C. 348(c)(1))

Dated: December 30, 1971.

R. E. DUGGAN,  
Acting Associate Commissioner  
for Compliance.

[FR Doc. 72-400 Filed 1-10-72; 8:50 am]

SUBCHAPTER C—DRUGS

PART 148e—ERYTHROMYCIN

**Erythromycin—Sulfonamide Combination Products for Oral Administration; Final Order Ruling on Objections and Requests**

An order was published in the FEDERAL REGISTER of September 27, 1969 (34 F.R. 14890) (DESI 8957), to become effective in 40 days, amending Part 148e of the antibiotic drug regulations by repealing provisions for certification of combination drugs containing erythromycin and triple sulfonamides for oral administration. Thirty days were allowed for filing proper objections to the order, and a showing of reasonable grounds for a hearing.

Objections and requests for a hearing were submitted by Eli Lilly and Company and Abbott Laboratories on October 27, 1969. Eli Lilly subsequently amended its request by letter dated December 2, 1969; Abbott Laboratories amended its request on June 5, 1970, in response to the order promulgated May 8, 1970 (35 F.R. 7250), which established the procedural and interpretive rules applicable to requests for hearing. The Upjohn Co., by letter dated November 25, 1969, adopted and incorporated by reference the objections filed by Eli Lilly and Abbott. Subsequently by notice published in the FEDERAL REGISTER on November 8, 1969 (34 F.R. 8087) and January 3, 1970 (35 F.R. 77) the effective date of the order was postponed pending a rule on the objections and requests for hearing filed.

The medical presentations of both firms have been considered, and the Commissioner of Food and Drugs concludes that there is no genuine and substantial issue of fact requiring a hearing and that the legal arguments offered are insubstantial, all as explained in more detail below.

I. *The drugs.* The drugs involved contain erythromycin and triple sulfonamides in the following combinations:

ABBOTT LABORATORIES

Erythrocin Ethyl Succinate-Sulfas Chewable Tablets and Granules. These contain erythromycin ethylsuccinate together with sulfadiazine, sulfamerazine and sulfamethazine in a 1:1:1 ratio.

Erythrocin Stearate-Sulfas Filmtabs. This contains erythromycin stearate, with sulfadiazine, sulfamerazine and sulfamethazine in a 1:1:1 ratio.

Each product contains, per unit dose (tablet or 5 cc. teaspoon), 125 mg. erythromycin and 500 mg. triple sulfas.

ELI LILLY AND CO.

Iosone Sulfa, for oral suspension and tablets. These contain 200 mg. erythromycin estolate, with 500 mg. triple sulfas consisting of sulfadiazine, sulfamerazine, and sulfamethazine in a 1:1:1 ratio.

Ilotycin-Sulfa Tablets, which contains 79 mg. erythromycin with 333 mg. triple sulfas as sulfadiazine, sulfamerazine, and sulfamethazine in a 1:1:1 ratio.

UPJOHN CO.

Erythrosulfa Tablets, containing erythromycin, with sulfadiazine, sulfamerazine, and sulfamethazine in a 1:1:1 ratio. Each unit dose contains 100 mg. erythromycin and 250 mg. triple sulfas.

II. *Recommended uses and rationale.* These products are recommended for use in mixed infections, infections more susceptible to the combination than to either component alone, and for gram-negative and/or mixed infections of the urinary tract.

The rationale for use in "mixed infections", seems to be that the components complement each other in that the erythromycin acts against gram-positive and the triple sulfas against gram-negative organisms. With respect to "infections more susceptible to the combination than to either alone," the rationale apparently is supplementation of the effect of erythromycin with the effect of triple sulfas so that concentrations that are suboptimal for either agent are effective in combination.

The recommended treatment schedules for the various products vary from 948 mg. to 1.6 grams of erythromycin per day; all products recommend a total dosage of 4 grams of triple sulfas per day.

III. *The data to support claims of effectiveness—(a) Unpublished studies.* In response to the notice, Abbott submitted two volumes with eight appendixes containing a summary of 226 patients treated with erythromycin-sulfonamide combination drugs as compared to 346 patients treated with erythromycin alone; in vitro studies on erythromycin-sulfonamide combinations; and, blood-level data.

The in vitro data does not rise to the level of adequate and well-controlled clinical investigations and cannot be extrapolated to human experience. The blood level data contained some data respecting a proposed sulfonamide formulation in a 1:1:4 ration; this is irrelevant to the products' sulfonamide formulation in a 1:1:1 ratio. The data which relates to the 1:1:1 preparation involved a dose twice that recommended in the package insert; no comparison is made with the blood levels produced by erythromycin alone.

The clinical data shows a total cured and improved rate of 90.51 percent for those patients treated with the combination as compared with a total cured and improved rate of 95.07 percent for the patients treated with erythromycin alone. This does not establish the superiority of the combination, but of one of the components. In addition, the data are unreliable because of a wide variability in

clinical diagnosis; a lack of post-treatment bacteriologic work with the exception of one investigator working with a 1:1:4 ratio sulfonamide product, which is irrelevant here; the data is pooled data drawn from dissimilar studies in which clinical observations were not made consistently; so many cultures showed normal flora that it is evident that many of the infections must have been viral in etiology and therefore nonresponsive to either antibacterial therapy, and there is no way of knowing the distribution of viral infections in both groups; some of the patients received rectal or intramuscular erythromycin as well as oral erythromycin. No valid conclusions can be based on such uncontrolled data.

With respect to the claim that the erythromycin-sulfa combination is effective in urinary infections with gram-negative and gram-positive mixed infections, Abbott states that a study submitted to the FDA showed a significantly greater number of sterile post-therapy cultures when the isolates in pretherapy cultures were all gram-positive or mixed, when treated with a combination rather than with sulfa alone.

Although it is not further identified, the study referred to is believed to be a composite study submitted by Abbott in a 1968 Experience Report, in which four separate investigations were conducted. A detailed protocol of this study was not submitted. Therefore, FDA does not know the doses used in the study, nor the identity of the sulfa used.

In this study, a total of 63 patients with urinary tract infections were treated with erythromycin-sulfa; 67 were treated with sulfa alone. Adverse drug reactions were higher on the combination (7.6 percent), than on sulfa alone (3 percent). By the monitor's evaluation, the cure rate for the combination (28.6 percent) was much lower than for sulfa (40 percent). Over 80 percent of the organisms cultured before therapy were gram-negative, as would be expected. 77.4 percent of the gram-negative organisms were eradicated after therapy with sulfa, but only 63.2 percent after the combination. Only 3 percent of the infections treated (2 patients in each group) were due to "mixed" gram-negative and gram-positive organisms. The statement that "a significantly greater number of sterile posttherapy cultures when the isolates in pretherapy cultures were all gram-positive or mixed, when treated with a combination rather than with sulfa alone," is unsupported in that over 80 percent of the urinary infections were neither gram-positive nor mixed, and in this large percentage (as in the group as a whole), the combination was considerably less effective than sulfa alone.

(b) *Published studies.* Lilly specifically referred to two published studies which purport to establish that antibiotic sulfonamide combination products are effective. Neither study supports the claimed superiority of erythromycin-sulfonamide products, however, The Nilson, et al. study: "Acute Otitis Media:

Treatment Results in Relation to Bacterial Etiology," *Pediatrics* 43(3): 351-358 (Mar.), 1969, compared penicillin V, penicillin V plus triple sulfa in a 1:1:1 ratio, and Ampicillin in 306 children with otitis media. The authors concluded that either penicillin plus sulfonamide or ampicillin had a better therapeutic response than penicillin V alone. This study is not relevant here.

The second study, Howie and Plousard: The "In Vivo Sensitivity Test"—"Bacteriology of Middle Ear Exudate During Antimicrobial Therapy in Otitis Media," *Pediatrics* 44:940-944 (Dec.), 1969, compared penicillin with sulfonamides, penicillin, ampicillin, erythromycin, erythromycin plus sulfonamides, triple sulfas, sulfamethoxazole or sulfadimethoxine, and tetracycline in unequal groups of children. The authors concluded ampicillin, penicillin-sulfa, and erythromycin-sulfas to be the most bacteriocidal. The authors also state that the information "was not collected in a large double blind study with multiple safeguards against the opinions of the authors influencing the results." No conclusion can be drawn from his uncontrolled study.

Abbott referred to 24 references from the published literature. All but one of the references are not entitled to consideration for various reasons, including the lack of controls, employment of different doses, different drugs: One study is relevant. Lenoski, et al.: "Drug Trials in Acute Otitis Media," *Curr. Ther. Res.* 10:630, December 1968. In this study 293 children with acute otitis media were treated on a randomized basis with either erythromycin alone, Abbott's fixed combination of erythromycin succinate-triple sulfas, triple sulfas alone, ampicillin or placebo. Ninety-four percent of those on erythromycin alone were cured; 87.5 percent on erythromycin-sulfa combined were cured. The authors concluded that addition of triple sulfonamide to erythromycin did not improve the outcome of the acute purulent cases at 14 days regardless of the dose schedule used for the combination drug. Moreover, the combination drug was associated with 2.6 percent incidence of skin rashes which were typical allergic drug reactions. In this controlled study, erythromycin alone was shown to be more effective than the fixed combination.

A published controlled study which was not referred to by either Abbott or Lilly is Hughes and Collier: "Streptococcal Pharyngitis," *Am. J. Dis. Child.* 118: 700-707, 1969. In this study, children with beta-hemolytic streptococcal pharyngitis were treated with Abbott's erythromycin-sulfas or with erythromycin alone. The cure rate for erythromycin alone was 84.2 percent; for the combination, 68.5 percent.

Thus, there is a lack of substantial evidence consisting of adequate and well-controlled clinical studies that the fixed combination products consisting of erythromycin plus sulfonamides will have the result claimed for them. On the contrary, the controlled studies establish

that the fixed combination products are less effective than either the erythromycin or sulfonamide components.

IV. *Legal objections.* The legal objections raised to the proposed order have been resolved in "Upjohn Co. v. Finch," 422 F. 2d 944 (C.A. 6, 1970); "Pfizer, Inc. v. Richardson," 434 F. 2d 536 (C.A. 2, 1970); and "Pharmaceutical Manufacturers Association v. Richardson," 318 F. Supp. 301 (D. Del., 1970). The contentions that Abbott's products are not subject to the efficacy review under the statute because they were not reviewed by the NAS-NRC and because the products were approved for marketing after the 1962 Drug Amendments are insubstantial. The NAS-NRC was advisory to the Food and Drug Administration and their review of a particular product's claims is not a condition precedent to the FDA's action in reviewing claims of drug effectiveness. In addition, the NAS-NRC did evaluate the other firms' products. All the triple sulfas are identical and all in a 1:1:1 ratio; the active forms of erythromycin are identical in all three firms' products although there are variations in the formulations. The NAS-NRC concluded that there is an "absence of clinical evidence supporting the use of erythromycin-sulfonamides in the therapy of any disease." The Food and Drug Administration agrees. In this connection, the fact that Abbott's products were approved for marketing in 1966 and 1967 does not compel the conclusion that these products should remain on the market while the competitive products reviewed by NAS-NRC are removed. The NAS-NRC review of erythromycin-sulfonamide products and the controlled studies establishing the combination to be less effective than its components are "new information" within the meaning of the statute.

V. *Findings.* The Commissioner, based on the review of the medical documentation offered to support the claims of efficacy for these fixed combination erythromycin-sulfonamide products, finds that Abbott, Lilly and Upjohn have failed to present substantial evidence of effectiveness for these products. In recognition of the known hazards associated with the use of each component, e.g. hypersensitivity reactions, gastrointestinal irritation, and overgrowth of non-susceptible bacteria or fungi from erythromycin, and sensitization reactions from sulfonamides including drug fever, serum sickness, hematologic reactions including aplastic anemia, and renal damage, the regulations for certification of antibiotic drugs should be amended to delete these fixed combination erythromycin-sulfonamide products from the list of drugs acceptable for certification. The Commissioner further finds that the certificates of safety and effectiveness heretofore issued for these fixed combination erythromycin-sulfonamide products should be revoked on the basis of a lack of substantial evidence of effectiveness and an unwarranted hazard from this fixed combination antibiotic therapy.

Therefore, pursuant to the provisions of the Federal Food, Drug, and Cosmetic

Act (secs. 502, 507, 701, 52 Stat. 1050-53, as amended, 59 Stat. 463, as amended, 76 Stats. 785-787; 21 U.S.C. 352, 357, 371), and under authority delegated to the Commissioner (21 CFR 2.120), notice is given that the order of September 27, 1969 (34 F.R. 14890), to the extent that the provisions contained therein conform to those of Part 148e as republished in the FEDERAL REGISTER of December 5, 1970 (35 F.R. 18513), will become effective 30 days after the date of publication hereof in the FEDERAL REGISTER to allow time for recall of outstanding stocks of effected drugs. Certificates of safety and effectiveness previously issued for such drugs for human use under these regulations will be revoked. No new certificates will be issued.

Dated: January 3, 1972.

SAM D. FINE,  
Associate Commissioner  
for Compliance.

[FR Doc. 72-350 Filed 1-10-72; 8:50 am]

## Title 29—LABOR

### Chapter XVII—Occupational Safety and Health Administration, Department of Labor

#### PART 1910—OCCUPATIONAL SAFETY AND HEALTH STANDARDS

##### Standard for Exposure to Asbestos Dust in Ship Repairing, Shipbuilding, Shipbreaking, and Longshoring

Pursuant to section 6(c) of the Williams-Steiger Occupational Safety and Health Act of 1970 (84 Stat. 1596; 29 U.S.C. 655) and Secretary of Labor's Order No. 12-71 (36 F.R. 8754), 29 CFR 1910.13, 1910.14, 1910.15, and 1910.16 are hereby amended as set forth below, in order to prescribe an emergency temporary standard concerning the exposure of employees to asbestos dust.

Sections 1910.13, 1910.14, 1910.15, and 1910.16 adopt, and extend the applicability of, maritime safety and health standards originally published in 29 CFR Parts 1501, 1502, 1503, and 1504, now redesignated as 29 CFR Parts 1915, 1916, 1917, and 1918 (see 36 F.R. 25232). Those standards permit the exposure of employees to concentrations of asbestos dust so high as to constitute a great danger to the employees. The immediate adoption of the emergency temporary standard set forth below, which is the same as that promulgated for industries in general on December 7, 1971 (36 F.R. 23207) is necessary to protect employees from that danger.

In addition, 29 CFR 1910.93a (36 F.R. 23208) is amended by correcting a clerical error in paragraph (g) thereof.

Part 1910 of Title 29 of the Code of

Federal Regulations is amended as follows:

1. In § 1910.13, a new paragraph (c) is added, reading as follows:

#### § 1910.13 Ship repairing.

(c) The standards prescribed in § 1910.93a shall apply in the case of exposure of any employee to asbestos dust, in lieu of any different standards otherwise required by Part 1915 of this chapter (formerly Part 1501 of this title).

2. In § 1910.14, a new paragraph (c) is added, reading as follows:

#### § 1910.14 Shipbuilding.

(c) The standards prescribed in § 1910.93a shall apply in the case of the exposure of any employee to asbestos dust, in lieu of any different standards otherwise required by Part 1916 of this chapter (formerly Part 1502 of this title).

3. In § 1910.15, a new paragraph (c) is added, reading as follows:

#### § 1910.15 Shipbreaking.

(c) The standards prescribed in § 1910.93a shall apply in the case of exposure of any employee to asbestos dust, in lieu of any different standards otherwise required by Part 1917 of this chapter (formerly Part 1503 of this title).

4. In § 1910.16, a new paragraph (c) is added, reading as follows:

#### § 1910.16 Longshoring.

(c) The standards prescribed in § 1910.93a shall apply in the case of exposure of any employee to asbestos dust, in lieu of any different standards otherwise required by Part 1918 of this chapter (formerly Part 1504 of this title).

5. In § 1910.93a (36 F.R. 23208), paragraph (g) is revised to read as follows:

#### § 1910.93a Asbestos dust.

(g) All cleanup of asbestos dust shall be performed by vacuum cleaners. No dry sweeping or blowing of dust shall be performed.

(Sec. 6(c), 84 Stat. 1596; 29 U.S.C. 655. Secretary's Order No. 12-71, 36 F.R. 8764)

**Effective date.** These amendments shall become effective immediately upon publication in the FEDERAL REGISTER (1-11-72).

Signed at Washington, D.C., this 6th day of January 1972.

G. C. GUENTHER,  
Assistant Secretary of Labor.

[FR Doc. 72-401 Filed 1-10-72; 8:40 am]

## Title 40—PROTECTION OF ENVIRONMENT

### Chapter I—Environmental Protection Agency

#### SUBCHAPTER E—PESTICIDES PROGRAMS

#### PART 180—TOLERANCES AND EXEMPTIONS FROM TOLERANCES FOR PESTICIDE CHEMICALS IN OR ON RAW AGRICULTURAL COMMODITIES

##### Dimethoate

A petition (PP 0F0999) was filed by the American Cyanamid Co., Agricultural Division, Post Office Box 400, Princeton, NJ 08540, in accordance with provisions of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 346a), proposing establishment of tolerances for residues of the insecticide dimethoate (O,O-dimethyl-S-(N-methylcarbamoylmethyl) phosphorodithioate) including its oxygen analog (O,O-dimethyl-S-(N-methylcarbamoylmethyl) phosphorothioate) in or on the raw agricultural commodities cucumbers at 2 parts per million, sorghum forage at 0.5 part per million, and sorghum grain at 0.1 part per million (negligible residue).

The petitioner subsequently amended the petition by withdrawing the request for a tolerance for residues in or on cucumbers and reducing the proposed tolerance for residues in or on sorghum forage to 0.2 part per million.

Prior to December 2, 1970, the Secretary of Agriculture certified that the pesticide is useful for the purpose for which tolerances are proposed, and the Fish and Wildlife Service, Department of the Interior, stated that it has no objection to the proposed tolerances.

Part 120, Chapter I, Title 21 was redesignated Part 420 and transferred to Chapter III (36 F.R. 424). Subsequently, Part 420, Chapter III, Title 21 was redesignated Part 180 and transferred to Subchapter E, Chapter I, Title 40 (36 F.R. 22369).

Based on consideration given data submitted in the petition and other relevant material, it is concluded that:

1. Establishes tolerances for residues of the pesticide in eggs, meat, milk, and poultry are adequate to cover combined residues from the proposed and established uses.

2. The proposed tolerance of 0.1 part per million on sorghum grain is not a negligible residue.

3. The tolerances established by this order will protect the public health.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (sec. 408(d)(2), 68 Stat. 512; 21 U.S.C. 346a(d)(2)), the authority transferred to the Administrator of the Environmental Protection Agency (35 F.R. 15623), and the authority delegated by the Administrator to the Deputy Assistant Administrator for Pesticides Programs (36 F.R. 9038), § 180.204 is amended by revising the paragraphs