Issued in Des Plaines, Illinois, on December 20, 1983.

Monte R. Belger,

Acting Director,

Great Lakes Region.

[FR Doc. 84-55 Filed 1-3-84; 8:45 am]

BILLING CODE 4910-13-M

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 73

[Docket No. 83C-0179]

Listing of Color Additives for Coloring Contact Lenses

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the color additive regulations to provide for the safe use in coloring contact lenses of the color polymeric reaction products formed by chemically bonding certain dyes, used singly or in combination, with poly(hydroxyethyl methacrylate). The reaction products are called "poly(hydroxyethyl methacrylate)-dye copolymers" in the listing regulation. The agency is taking this action in response to a petition filed by Ciba Vision Care.

DATES: Effective February 6, 1984; objections by February 3, 1984.

ADDRESS: Written objections to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: John L. Herrman, Bureau of Foods (HFF-334), Food and Drug Administration, 200 C St. SW., Washington, DC 20204, 202-472-5740.

SUPPLEMENTARY INFORMATION: In a notice published in the **Federal Register** of July 5, 1983 (48 FR 30758), FDA announced that a color additive petition (CAP 3C0174) has been filed by Ciba Vision Care, P.O. Box 105069, Atlanta, GA 30348, proposing "that the color additive regulations be amended to provide for the safe use of the following dyes chemically bonded to the lens polymer, singly or in various combinations, for coloring contact lenses: Reactive Blue 21 (CAS Reg. No. 73049-92-0), Reactive Black 5 (CAS Reg. No. 17095-24-8), Reactive Yellow 15 (CAS Reg. No. 60958-41-0), and Reactive Orange 78 (CAS Reg. No. 68189-39-9)." The petition was filed under section 706 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 376).

The colored polymeric reaction products that are subject of this petition are formed when one or more of the dyes listed in § 73.3121(a) (21 CFR 73.3121(a)) are bonded with poly(hydroxyethyl methacrylate) on the front surface of a contact lens to form a thin layer of colored polymeric material on that surface. This polymeric material colors the contact lens.

Under the Medical Device Amendments of 1976 (Pub. L. 94-295), a color additive for use in a medical device must be listed when the color additive comes in direct contact with the body for a significant period of time (section 706(a) of the act). The polymeric reaction products of the reactive dyes and poly(hydroxyethyl methacrylate), called "poly(hydroxyethyl methacrylate)-dye copolymers" in § 73.3121, are color additives within the meaning of section 201(t) of the act (21 U.S.C. 321(t)) because they are substances made by a process of synthesis or similar artifice, and because they are capable of imparting color to food, drugs, cosmetics, or the human body if added or applied thereto. In the use considered here, the reactive dyes are merely starting materials and not color additives subject to section 706 of the act. In the reaction process that occurs in bonding the reactive dyes to the poly(hydroxyethyl methacrylate), the reactive dyes cease to exist as separate entities.

The use of the poly(hydroxyethyl methacrylate)-dye copolymers as color additives in contact lenses is subject to regulation under section 706(a) of the act. The lenses that have this colored polymeric material on their front surfaces are intended to be placed on the eye for several hours a day, each day, for 1 year or more. These color additives accordingly will come in direct contact with the body for a significant period of time. Consequently, the use of the color additives presented in the petition now before the agency is subject to the statutory listing requirement.

To establish that the color additives are safe for use in contact lenses, the petitioner submitted various toxicity data. In a primary ocular irritation study with extracts of lens material containing the color additives, and in a 21-day ocular irritation study with contact lenses tinted with the color additives, both of which were done in rabbits, neither the lens containing the color additives nor the extracts of the colored lens material caused ocular irritation under the conditions of these tests. The agency has also reviewed data regarding the toxicity of potential impurities, such as unbound reactive dye starting materials, remaining in the lens. The reactive dye starting materials, being of lower molecular weight than the polymeric color additive, would be more readily absorbed into the body than the color additive and would thus be expected to show a greater toxic effect. FDA has concluded that, as a worst case, any material migrating from the color additive in the lens would not pose a greater safety concern than if the reactive dye starting materials were placed in the lens unbound, and all migrated into the eye over a 1-year period. This amount of migration would be equivalent to 5 to 45 micrograms of reactive dye starting material per lens or a total of 27 to 250 nanograms per day for both eyes, depending on the reactive dye used. The petitioner conducted cytotoxicity studies in which serial dilutions of the individual reactive dyes were applied directly to L-929 mouse fibroblast cells. For the reactive dye used in the greatest amounts, no toxic effect was seen at a concentration 1,300 times the concentration that would be in the eyes if 250 nanograms migrated into the eyes per day. All other reactive dyes showed no toxic effect with even greater factors above the worst case eye concentration, ranging up to 61,000 times the concentration that would be in the eyes from 27 nanograms per day.

On the basis of these studies, FDA concludes that the safety margin is sufficiently large that, for any foreseeable formulation, a limitation on the amount of these color additives that may be present on the lens, beyond the limitation that only that amount necessary to accomplish the intended technical effect may be used, is not required.

FDA received an anonymous comment in response to the notice of filing of this petition. The person making the comment claims that the dye-polymer reaction is reversible, resulting in the release of toxic dyes into the eye during the lifetime of the contact lens, but did not provide data to support that claim. Information in the petition shows that the dye-polymer reaction is reversible in alkali, but that the polymeric color additive is highly stable under the physiological conditions of the eye. The agency has also searched the toxicity literature and has found no data supporting the claim regarding the toxicity of the materials that would be released if the binding reaction were reversed. The agency therefore finds no basis for the assertions in the comment.

FDA, having reviewed the anonymous comment, data in the petition, and other

relevant material, concludes that there is a reasonable certainty that no harm will result from the proposed use of the reaction products of poly(hydroxyethyl methacrylate) with Reactive Black 5, Reactive Blue 21, Reactive Orange 78, and Reactive Yellow 15, used singly or in various combinations, for coloring contact lenses. To further assure the safety of the use of these color additives, FDA is establishing a requirement that the manufacturer wash the lens to remove unbound reactive dyes. The agency also concludes that the poly(hydroxyethyl methacrylate)-dye copolymers listed in § 73.3121 are suitable for their intended use. On the basis of factors listed in § 71.20(b) (21 CFR 71.20(b)), the agency concludes that certification of the color additive is not necessary for the protection of the public health.

In accordance with § 71.15(a) (21 CFR 71.15(a)), the petition and the documents that FDA considered and relied upon in reaching its decision to approve the petition are available for inspection at the Bureau of Foods (address above) by appointment with the information contact person listed above. As provided in § 71.15(b), the agency will delete from the documents any materials that are not available for public disclosure before making the documents available for inspection.

The agency has previously concluded that this action will not have a significant impact on the human environment and that an environmental impact statement is not required. No new information or comments have been received that would alter the agency's previous determination that there is no significant impact on the human environment, and that an environmental impact statement is not required.

List of Subjects in 21 CFR Part 73

Color additives, Cosmetics, Drugs, Medical devices.

PART 73—LISTING OF COLOR ADDITIVES EXEMPT FROM CERTIFICATION

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 701(e), 706, 70 Stat. 919 as amended, 74 Stat. 399–407 as amended (21 U.S.C. 371(e), 376)) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 5.10), Part 73 is amended by adding new § 73.3121 under Subpart D, to read as follows:

§ 73.3121 Poly(hydroxyethyl methacrylate)-dye copolymers.

(a) *Identity.* The color additives are formed by reacting one or more reactive dyes listed in this paragraph with poly(hydroxyethyl methacrylate), so that the sulfate group (or groups) of the dye is replaced by an ether linkage to the poly(hydroxyethyl methacrylate). The dyes are (1) Reactive Black 5 [2,7-naphthalenedisulfonic acid,4-amino-5-hydroxy-3,6-bis[(4-[(2-(sulfooxy)ethyl)sulfonyl)-phenyl)azo)-, tetrasodium salt] (CAS Reg. No. 17095–24–8); (2) Reactive Blue 21 [copper, (29*H*,31*H*-phthalocyaninato(2-)-*N*(29),*N*(30),*N*(31),*N*(32))-, sulfo[(4-[(2-sulfooxy)ethyl)sulfonyl)phenyl)amino) sulfonyl derivs] (CAS Reg. No. 73049–92–0); (3) Reactive Orange 78 [2-naphthalene-sulfonic acid,7-(acetyl-amino)-4-hydroxy-3-[(4-[(2-(sulfooxy)-ethyl)sulfonyl)phenyl)azo)-] CAS Reg. No. 68189–39–9); and (4) Reactive Yellow 15 [benzensulfonic acid,4-[4,5-dihydro-4-[(2-methoxy-5-methyl-4-[(2-(sulfooxy)ethyl)sulfonyl)phenyl)azo)-3-methyl-5-oxo-1*H*-pyrazol-1-yl)-] (CAS Reg. No. 60958–41–0).

(b) *Uses and restrictions.* (1) The substances listed in paragraph (a) of this section may be used to color contact lenses in amounts not to exceed the minimum reasonably required to accomplish the intended coloring effect.

(2) As part of the manufacturing process, the lenses containing the color additives are thoroughly washed to remove unbound reactive dyes.

(3) Authorization and compliance with this use shall not be construed as waiving any of the requirements of sections 510(k), 515, and 520(g) of the Federal Food, Drug, and Cosmetic Act (the act). A person intending to introduce a device containing a poly(hydroxyethyl methacrylate)-dye copolymers listed under this section into commerce shall submit to the Food and Drug Administration either a premarket notification in accordance with Subpart E of Part 807 of this chapter, if the device is not subject to premarket approval, or submit and receive approval of an original or supplemental premarket approval application if the device is subject to premarket approval.

(c) *Labeling.* The label of the color additive shall conform to the requirements of § 70.25 of this chapter.

(d) *Exemption from certification.* Certification of this color additive is not necessary for the protection of the public health, and therefore the color additive is exempt from the certification requirements of section 706(c) of the act.

Any person who will be adversely affected by the foregoing regulation may at any time on or before February 3, 1984 file with the Dockets Management Branch (address above) written objection thereto. Objections shall show how the person filing will be adversely affected by the regulation., specify with particularity the provisions of the regulation deemed objectionable, and state the grounds for the objections. Objections shall be filed in accordance with the requirements of 21 CFR 71.30. If a hearing is requested, the objections shall state the issue for the hearing, shall be supported by grounds factually and legally sufficient to justify the relief sought, and shall include a detailed description and analysis of the factual information intended to be presented in support of the objections in the event that a hearing is held. Three copies of all documents shall be filed and shall be identified with the docket number found in the brackets in the heading of this document. Any objections received in response to the regulation may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Effective date. This regulation shall become effective February 6, 1984, except as to any provisions that may be stayed by the filing of proper objections. Notice of the filing of objections or lack thereof will be announced by publication in the **Federal Register.**

(Secs. 701(e), 706, 70 Stat. 919 as amended, 74 Stat. 399–407 as amended (21 U.S.C. 371(e), 376))

Dated: December 28, 1983.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 84–81 Filed 1–3–84; 8:45 am]

BILLING CODE 4160–01–M

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21 CFR Part 452

[Docket No. 83N–0285]

Antibiotic Drug; Updating and Technical Changes; Correction

AGENCY: Food and Drug Administration.

ACTION: Final rule; correction.

SUMMARY: The Food and Drug Administration (FDA) is correcting the final rule that amended the antibiotic drug regulations by making corrections, updatings, and minor technical changes. This document corrects the amendatory language to clairfy the technical change that was made in § 452.510b(a)(1).

EFFECTIVE DATE: November 8, 1983.

FOR FURTHER INFORMATION CONTACT: Joan M. Eckert, National Center for Drugs and Biologics (HFN–140), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–443–4290.

SUPPLEMENTARY INFORMATION:

§ 452.510b [Corrected]

In FR Doc. 83-30122 in the issue for Tuesday, November 8, 1983 (48 FR 51292), on page 51292 in the right column, amendment 7 is corrected to read "Part 452 is amended in § 452.510b by revising the fifth sentence and deleting the sixth sentence in paragraph (a)(1); by revising paragraph (a)(3)(i)(*b*); and by revising paragraph (b)(2) to read as follows:"

(This correction clarifies that only sentences five and six in §452.510b(a)(1) are affected. Even though sentence four is restated in the amendment, it is not changed. Nor is the last sentence, which is not restated, changed.)

Dated: December 28, 1983.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 84-30 Filed 1-3-84; 8:45 am]

BILLING CODE 4160-01-M

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21 CFR Part 558

New Animal Drugs for Use in Animal Feeds; Tylosin

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a supplemental new animal drug application (NADA) filed for International Nutrition, Inc., providing for manufacturing a 20-gram-per-pound tylosin premix. The premix is used to make finished feeds for swine, beef cattle, and chickens.

EFFECTIVE DATE: January 4, 1984.

FOR FURTHER INFORMATION CONTACT: Benjamin A. Puyot, Bureau of Veterinary Medicine (HFV-130), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4913.

SUPPLEMENTARY INFORMATION: International Nutrition, Inc., 6664 L St., Omaha, NE 68117, is sponsor of a supplement to NADA 95-551 submitted on its behalf by Elanco Products Co. This supplement provides for the manufacture of 20-gram-per-pound premixes subsequently used to make finished feeds for swine, beef cattle, and chickens for use as in 21 CFR 558.625(f)(1) (i) through (vi). Based on the data and information submitted, the supplement is approved and the regulations are amended to reflect the approval. The basis for approval of this supplement is discussed in the freedom of information summary.

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 determined pursuant to 21 CFR 25.24(d)(1)(i) (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 settlement is required.

List of Subjects in 21 CFR Part 558

Animal drugs, Animal feeds.

PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

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), Part 558 is amended in § 558.625 by revising paragraph (b)(3), to read as follows:

§ 558.625 Tylosin.

* * * * *

(b) * * *

(3) To 043733: 4 grams per pound, paragraph (f)(1)(vi)(*a*) of this section; 10 grams per pound, paragraph (f)(1) (i), (iii), (iv), and (vi) of this section; 20 grams per pound, paragraph (f)(1) (i) through (vi) of this section.

* * * * *

Effective date. January 4, 1984.

(Sec. 512(i), 82 Stat. 347 (21 U.S.C. 360b(i)))

Dated: December 22, 1983.

Robert A. Baldwin,

Associate Director for Selective Evaluation.

[FR Doc. 84-27 Filed 1-3-84; 8:45 am]

BILLING CODE 4160-01-M

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21 CFR Part 558

New Animal Drugs for Use in Animal Feeds; Monensin and Virginiamycin

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is amending the animal drug regulations to reflect approval of a supplemental new animal drug application (NADA) filed by SmithKline Animal Health Products, providing for safe and effective use of separately approved monensin and virginiamycin premixes in making a combination broiler chicken feed. The feed is used for prevention of coccidiosis and increased rate of weight gain.

EFFECTIVE DATE: January 4, 1984.

FOR FURTHER INFORMATION CONTACT: Lonnie W. Luther, Bureau of Veterinary Medicine (HFV-128), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4317.

SUPPLEMENTARY INFORMATION: SmithKline Animal Health Products, Division of SmithKline Beckman Corp., 1600 Paoli Pike, West Chester, PA 19380, filed supplemental NADA 122-481 providing for use of separately approved monensin sodium (Coban®) and virginiamycin (Stafac®) premixes in making a combination broiler feed containing 90 to 110 grams of monensin per ton and 5 to 15 grams of virginiamycin per ton. The feed is intended for use as an aid in the prevention of coccidiosis and for increased rate of weight gain. The original approval provides for a combination broiler feed containing 90 to 110 grams of monensin per ton and 5 grams of virginiamycin per ton for use as an aid in the prevention of coccidiosis and for increased rate of weight gain and improved feed efficiency. The premixes are approved for individual use in broiler feed at the same dosage ranges and for the same claims now provided for in combination. The supplemental NADA is approved and the regulations are amended accordingly. The basis for approval is discussed in the freedom of information summary.

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 determined pursuant to 21 CFR 25.24(d)(1)(ii) (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.

List of Subjects in 21 CFR Part 558

Animal drugs, Animal feeds.

PART 558—NEW ANIMAL DRUGS FOR USE IN ANIMAL FEEDS

Therefore, under the Federal Food, Drug, and Cosmetic Act (sec. 512(i), 82 Stat. 347 (21 U.S.C. 360b(i))) and under