[Airspace Docket No. 72-EA-68]

PART 71—DESIGNATION OF FEDERAL AIRWAYS, AREA LOW ROUTES, CONTROLLED AIRSPACE, AND REPORTING POINTS

PART 73—SPECIAL USE AIRSPACE

Alteration of Restricted Area and Continental Control Area and Designation of Transition Area

On July 28, 1972, a notice of proposed rule making (NPRM) was published in the FEDERAL REGISTER (37 F.R. 15170) stating that the Federal Aviation Administration (FAA) was considering amendments to Parts 71 and 73 of the Federal Aviation Regulations that would alter Restricted Area R-5203 at Oswego, N.Y., and the continental control area and designate a transition area at Oswego, N.Y.

Interested persons were afforded an opportunity to participate in the proposed rule making through the submission of comments. No comments were received on the airspace actions proposed.

In consideration of the foregoing, Parts 71 and 73 of the Federal Aviation Regulations are amended, effective 0901 G.m.t., December 7, 1972, as hereinafter set forth.

1. § 71.151 (37 F.R. 2045) is amended by adding "R-5203 Oswego, N.Y."

2. § 71.181 (37 F.R. 2143) is amended by adding the Oswego, N.Y., transition area as follows:

OSWEGO, N.Y.

"That airspace extending upward from 1,200 feet AGL beginning at lat. 43°37'00' N., long. 76°45'00" W.; to lat. 43°24'00" N., long. 76°45'00" W.; to lat. 43°24'00" N., long. 78°00'00" W.; to lat. 43°37'00" N., long. 78°00'00" W.; to the point of beginning."

3. In § 73.52 (37 F.R. 2364) the Oswego, N.Y., Restricted Area R-5203 is amended by deleting designated altitude, time of designation, and using agency in their entirety and substituting the following therefor:

"Designated Altitudes. Surface to Flight Level 500."

"Time of Designation. Continuous."

"Controlling Agency. Federal Aviation Administration, Cleveland ARTC Center."

"Using Agency. Commander, 107th Fighter Group, Niagara Falls International Airport."

(Sec. 307(a), Federal Aviation Act of 1958, 49 U.S.C. 1348(a); sec. 6(c), Department of Transportation Act, 49 U.S.C. 1655(c))

Issued in Washington, D.C., on September 20, 1972.

H. B. HELSTROM,
Chief, Airspace and Air Traffic Rules Division.

[FR Doc.72-16382 Filed 9-26-72;8:45 am]

[Airspace Docket No. 71-EA-167]

PART 71—DESIGNATION OF FEDERAL AIRWAYS, AREA LOW ROUTES, CONTROLLED AIRSPACE, AND REPORTING POINTS

Designation of Transition Area; Correction

Correction

In F.R. Doc. 72-15254 appearing on page 18183 of the issue for Friday, September 8, 1972, in the definition of Warning Area W-107, Atlantic City, N.J., the second set of coordinates in the 14th line, now reading "39°05'10'"", should read "39°51'10'"".

Title 20—EMPLOYEES' BENEFITS

Chapter V—Manpower Administration, Department of Labor

PART 625—DISASTER UNEMPLOYMENT ASSISTANCE

On page 16104 of the FEDERAL REGISTER of August 10, 1972, there was published a notice of proposed rulemaking to revise § 625.9(c)(1) by providing for certain additional deductions from disaster unemployment assistance payable to an applicant. Interested persons were given 30 days in which to submit written data, views, or arguments regarding the proposed changes.

No objections have been received and the proposed amendments are hereby adopted without change and are set forth below.

Effective date: These amendments shall be effective 30 days after publication in the FEDERAL REGISTER.

Signed at Washington, D.C., this 21st day of September 1972.

J. D. HODGSON,
Secretary of Labor.

As amended, § 625.9(c)(1) reads as follows:

§ 625.9 Amount.

* * * * *

(c) *Deductions.* The disaster unemployment assistance payable to an applicant for a week shall be reduced by:

(1) The amount of any of the following that an applicant has received for the week or would receive for the week if he filed a claim or application therefor and took all procedural steps necessary under the appropriate law or insurance policy:

(i) Regular unemployment compensation, additional unemployment compensation, extended unemployment compensation, and any other unemployment compensation under a State or Federal unemployment compensation law, or

* * * * *

(vii) Any workmen's compensation by virtue of the death of the head of the household as the result of the major disaster in the major disaster area, prorated by weeks, if the applicant is within the provisions of § 625.8(a)(7).

[FR Doc.72-16443 Filed 9-26-72;8:50 am]

Title 21—FOOD AND DRUGS

Chapter I—Food and Drug Administration, Department of Health, Education, and Welfare

SUBCHAPTER A—GENERAL

PART 3—STATEMENTS OF GENERAL POLICY OR INTERPRETATION

Hexachlorophene as a Component in Drug and Cosmetic Products for Human Use

A notice of proposed rule making was published in the FEDERAL REGISTER of January 7, 1972 (37 F.R. 219), entitled "Antibacterial Ingredients in Drug and Cosmetic Products for Repeated Daily Human Use" and corrected in the FEDERAL REGISTER of January 25 1972 (37 F.R. 1116). In the January 7, 1972, document, the Commissioner of Food and Drugs proposed to establish guidelines, pending review by an OTC Drug Advisory Review Panel, for the continued marketing of products intended for repeated daily human use, and containing one or more antibacterial ingredients to achieve a specific drug or cosmetic purpose, to act as a preservative, or both. Interested persons were invited to submit comments on the proposal within 60 days.

For the purpose of clarity and specificity the term "antibacterial ingredients" is deleted from the title of this publication and is replaced by the term "hexachlorophene" in both the title and the text of the document. The qualification of "Repeated Daily" human use is also no longer pertinent and has been deleted. More than 250 comments were received regarding the January 7, 1972, notice of proposed rule making.

Since receipt of these comments, a number of infant deaths have occurred in France due to use of a baby powder accidentally contaminated with 6 percent hexachlorophene. The central nervous system lesions in these infants were identical to those that have been produced in experimental animals exposed to hexachlorophene. There remains no doubt that hexachlorophene is a potent human neurotoxin at high levels of use; e.g., 3 percent emulsion and 6 percent in powder.

Moreover, even under previously recommended conditions of use, there is new evidence that neurologic damage may be produced. Recent data from the University of Washington indicate that there is a positive correlation between three or more exposures to hexachlorophene bathing with 3 percent hexachlorophene emulsion and lesions found

in the brainstem in premature infants who died of unrelated causes. At present the agency has no evidence of toxicity from the use of 0.75 percent or below. However, prudence requires pending further research in the pathogenesis of the neurologic lesions the public be protected from exposure to unneeded hexochlorophene.

Information on the data from France, the University of Washington, and other information are on display in the office of the Hearing Clerk and may be seen during normal working hours in Room 6–88, 5600 Fishers Lane, Rockville, Md. 20852.

The following is a summary of comments received by the Food and Drug Administration:

1. Numerous comments indicated that the long years of use of hexachlorophene have established its safety. The Food and Drug Administration is aware that hexachlorophene has been considered to be safe for many years. It is only recently that information on hexachlorophene toxicity, including deaths, has become known at high levels.

2. Some comments stated that it unreasonable to extrapolate quanitative levels of toxicity from other species to man, and that the studies cited by the Food and Drug Administration are not sufficient to support the proposed limitation on hexachlorophene. There are now ample studies in man to show that toxic amounts of hexachlorophene can be absorbed through the skin of humans, especially damaged skin. Human toxicity reports include data on symptomatology, blood and tissue levels of hexachlorophene, and descriptions of neuropathologic lesions. The contention that the lesion is reversible following discontinuing hexachlorophene usage has not been shown to be true at high-level exposures to hexachlorophene. At sublethal exposures clinical followups will be needed to determine the extent of residual damages.

3. A comment stated that there remained unanswered questions regarding the meaning of changes in the white matter of brain found in monkeys washed with 3 percent hexachlorophene, and that similar changes have been described as occurring with other substances. The Commissioner of Food and Drugs concludes that there are still unanswered questions regarding the changes seen in the white matter of the brain, but the lesions found in the experimental animals and in humans after hexachlorophene exposure have been sufficiently consistent to indicate a predictable neurological effect. Prudence requires that pending further research of the pathogenesis of the white matter lesion, the public be protected from unneeded exposure to hexachlorophene.

4. Studies were submitted to show that blood levels of hexachlorophene in the general population are very low. The studies cited are characterized by lack of precise information on exposure. Moreover, even though the mean blood levels may be low, the upper extreme of the distribution includes high levels. Previous studies have established that 3 percent of the total dose of hexachlorophene applied to intact adult skin is absorbed, and that the rate of absorption is almost constant, from 0 to 120 hours after application. There is also evidence that skin of premature infants and damaged or burned skin permit accelerated absorption.

5. It was argued in some comments that there is evidence that the nonuse or abrupt curtailment of hexachlorophene is responsible for widespread outbreaks of staphylococcal infections in hospital nurseries. The control of nosocomial infections is best directed by the medical profession. Studies to date indicate that the control of infections in nurseries may be dealt with in a variety of ways provided that good infection control practices are in effect. There are data to show that some nurseries, where it was a standard procedure to bathe babies with products containing hexachlorophene have experienced an increase in staphylococcal infections when such products were discontinued; while, other nurseries are able to control nosocomial infections without the use of such products. The Commissioner concludes that it is in the public interest to require a prescription for all hexachlorophene containing products, except at preservative levels. This will enable physicians to weigh the risk of hexachlorophene toxicity against the efficacy of hexochlorophene in infection control. The prescription dispensing requirement for a drug is satisfied by a physician's order governing infection control procedures for a nursery or department under his direction. This includes the use of products for hand washing by physicians and paramedical personnel as well as bathing of babies; e.g., a drug dispensed by this means is silver nitrate used in the eyes of newborn infants.

6. One comment alleges that hexachlorophene is unquestionably effective for washing the face and is useful as a drug in treatment of acne. The comment further alludes to the effectiveness of such products by referral to the NAS/NRC rating of hexachlorophene products. The interpretation is erroneous. In the FEDERAL REGISTER of December 8, 1971 (36 F.R. 23330), the Food and Drug Administration published the Drug Efficacy Study evaluations (DESI 6270) rating such products effective for use as bacteriostatic skin cleanser, including surgical scrub. However, for use in the treatment of impetigo in newborns, other staphylococcal skin infections, cradle cap, and in helping to clear acne, these products are rated only as possibly effective. A rating of "possibly effective" means that there is little evidence of effectiveness for the given indication.

7. The opinion was offered that since the Food and Drug Administration considers a product containing 3 percent hexachlorophene appropriate for washing the hands of hospital personnel, it is appropriate for use in washing the hands of food handlers to prevent contamination of food. The use of 3 percent hexachlorophene preparations for hand washing by food handlers cannot be equated with its use for hand washing by surgeons or hospital personnel. Physicians in the hospital environment are treating patients who are under stressful conditions, which make them peculiarly susceptible to infection, and under conditions where pathogenic organisms are known to be prevalent and easily transmitted. The Food and Drug Administration acknowledges the need for food handlers to wash their hands thoroughly. Pending the conclusion of the OTC Review Panel other antibacterial agents will be available for use. The OTC Review Panel will review the safety and effectiveness of such agents.

8. It was suggested in a comment received that to apply a "caution" statement to a product known to be safe under reasonably anticipated use is deceptive to the consumer since it implies a hazard which does not exist. Other comments related to the nonapplicability of the proposed over-the-counter caution statement to products such as first-aid creams, suntan and sunburn lotions containing 0.75 percent hexachlorophene or less, which when used as directed are not intended to be rinsed from the skin surface. One firm specifically commented that industrial creams containing no more than 0.75 percent hexachlorophene, and intended to be used under conditions which require protection from exposure to solvents, should be allowed to be marketed for their intended use at the discretion of the user, provided adequate directions are conveyed to the user. The Commissioner of Food and Drugs concludes that the evidence is such that the questions regarding the warning statement are moot since the benefits of hexachlorophene in OTC products do not outweigh its potential hazard. The Commissioner concludes there is presently no justification for continued production or shipment of these OTC products.

9. One comment alleged hexachlorophene is a substance with a high potential for harm and low evidence of benefit. It further stated that consumer protection demands that products containing hexachlorophene at levels from 0.1 to 0.75 percent be dispensed by prescription only, and that products containing more than 0.75 percent be stricken from the market until their safety and efficacy are scientifically demonstrated. The Food and Drug Administration has reviewed data published by the Center for Disease Control, Department of Health, Education, and Welfare, in the "Morbidity and Mortality Weekly" Vol. 21, No. 30, July 29, 1972. This report shows that in some hospital nurseries which discontinued washing babies with hexachlorophene containing products there was a rise in the incidence of staphylococcal infections, thereby suggesting efficacy of hexachlorophene bathing in the control of staphylococcal nursery infection. The Commissioner concludes that hexachlorophene should be retained for use

when necessary as a bacteriostatic skin cleanser for the control of gram-positive infection as an interim measure until alternative, safer measures for gram-positive infection control have been developed. On the basis of the data from France and the University of Washington and the OTC Panel Review, preparations containing over 0.1 percent hexachlorophene are limited to prescription use.

10. Comments were received from manufacturers of specialty products, including one from a firm which incorporates hexachlorophene into plastic resins used for manufacturing products which come in direct contact with the skin. The comments allude to the inequity of the proposal which has created a question of safety regarding such products where topical application is not involved. The Food and Drug Administration has no information on the safety or effectiveness of these products and they may not fall within the purview of this order. Such products will be considered on an individual basis and if they are not subject to one of the laws administered by the Food and Drug Administration may nevertheless be subject to Federal Trade Commission or Environmental Protection Agency jurisdiction with respect to safety.

11. One comment recommends that the proposal be changed to specify the method by which the quantity of hexachlorophene, as an active ingredient or as a preservative, should be calculated in determining the percentage in the finished product. The Commissioner considers this comment valid and a provision has been added to establish a uniform method to calculate and declare the quantity of hexachlorophene in products.

12. A number of comments were received stating that because hexachlorophene is included in the category of OTC antimicrobials scheduled for review, the proposal reaches scientific conclusions which are presumably the function of the OTC Drug Advisory Review Panel. In addition, the comments stated that the statement of policy would cause a bias, and if adopted, would represent an unwarranted, unscientific, and injudicious, restriction prior to the panel's review, in that it would be awkward for the OTC Drug Advisory Review Panel to reach any conclusions which are in contrast to the statement of policy. In conjunction with this comment it is stated, as further support for the request to await the Advisory Committee review, that consideration should be given to the fact that in manufacturers' efforts to conform to the statement of policy, many products would be removed from the market or would be reformulated. Even with the most careful reformulations, and with due evidence of safety in the hands of the manufacturers, before issuance of the panel's monograph, many reformulated products may contain other ingredients which are subsequently questioned by the panel and would require additional reformulation. A more orderly situation, it is contended, would result if reformulation took place after manufacturers had the benefit of the panel's monograph, in order to avoid the possibility of multiple reformulations, confusion, and economic loss to manufacturers. The FDA OTC Antimicrobial Panel has met and reviewed available animal and human toxicity of hexachlorophene, including the recent data from France and the University of Washington. The interim recommendation of the Panel is that hexachlorophene is not safe for use as an active ingredient in OTC antimicrobial products. This statement of policy on hexachlorophene will apply pending any further panel recommendations or any new evidence on the safety or effectiveness of hexachlorophene. The Commissioner concludes that sufficient evidence is on hand to necessitate restrictive action of hexachlorophene containing products now, and that delay is unjustifiable.

13. A number of comments objected to the statement in the proposal that antibacterial ingredients used as substitutes for hexachlorophene in cosmetic products, as well as the finished product, must be adequately tested for safety prior to marketing, and that any such ingredient or product whose safety is not adequately substantiated will be deemed misbranded, unless it bears a conspicuous front panel statement that the product has not been adequately tested for safety and may be hazardous. No comment argued that a consumer product may properly be marketed without first substantiating its safety, but it was contended that the concept of an implied warranty of merchantability and fitness for purpose is a matter of civil liability under the Uniform Commercial Code that is outside the Food and Drug Administration's province. Concern was also expressed that the Food and Drug Administration was attempting to force premarketing clearance of cosmetics through this requirement of safety substantiation. The Commissioner does not agree with these comments. This requirement means only that the manufacturer or distributor must have adequate scientific data in his files to substantiate the safety of the ingredients he uses, and the final products in which they are used. Under present law, such data need not be submitted to the Food and Drug Administration, and if a manufacturer wishes voluntarily to submit it to FDA he need not await FDA approval prior to marketing a product. This requirement of adequate substantiation is intended to reflect the basic requirement under the Federal Food, Drug, and Cosmetic Act, that labeling may not be false or misleading in any particular, and that the failure to reveal material facts can be as misleading as the use of false statements. As the comments recognized, under the Uniform Commercial Code, the marketing of a product in itself constitutes an implied representation that the product is merchantable and reasonably fit for its intended purpose. The courts have held that a failure to adequately test a product to substantiate its safety, resulting in injury to the user, violates these implied warranties and also constitutes negligence. The Federal Trade Commission has similarly ruled that safety must be substantiated prior to marketing. Failure to follow this fundamental principle of substantiating the safety of both the ingredients and the finished product prior to marketing, without a prominent label statement advising the consumer of that fact, is therefore grossly misleading. Accordingly, this provision is retained in the final regulation.

14. Several comments expressed the opinion that many drugs containing hexachlorophene are generally recognized as safe and effective and/or are covered by one or both of the "grandfather" clauses in the Act, and thus that a new drug application may not be required for such products. For the reasons outlined in previous paragraphs, there are substantial questions about the safety of hexachlorophene. Although at one time hexachlorophene may have been generally recognized as safe and effective, recent toxicity data, together with questions raised about the usefulness of topical antibacterial ingredients, no longer permit this conclusion. The parameters, within which topical antimicrobial ingredients are generally recognized as safe and effective and not misbranded, are presently under consideration by a panel under the OTC Drug Review. Unless and until that panel issues its final report and a monograph is effective for this category of ingredients no products containing hexachlorophene will be permitted OTC, and an NDA will be required for all drugs containing hexachlorophene at higher than preservative levels. Since any change in formulation or labeling precludes reliance on the "grandfather" clauses, and since it is unlikely that any product containing hexachlorophene has not changed its formulation or labeling since 1962, or in any event will not be required to make such a change under this regulation, it is highly doubtful that there is any drug containing hexachlorophene which may claim "grandfather" protection. Accordingly, the Food and Drug Administration will institute regulatory action against any drug containing hexachlorophene for which an NDA is not submitted within the time period permitted by this regulation.

CONCLUSIONS

The limitations proposed for hexachlorophene preparations in the FEDERAL REGISTER of January 7, 1972 (37 F.R. 219), are inadequate to protect the public health. Since that time new data received by the FDA clearly establish the toxicity of hexachlorophene, especially on the skin of premature infants or damaged skin. On the other hand, data are also available which support the efficacy of hexachlorophene as an aid in control of staphylococcal infections in hospital nurseries (the CDC study cited in item 9 above). The Commissioner thus concludes, based on the current benefit to risk ratio, as follows:

1. Hexachlorophene may continue to be used in cosmetics and drug preparations as a preservative only at levels not to exceed 0.1 percent.

2. There are presently no data to support a safe and effective OTC use for hexachlorophene.

3. Hexachlorophene as a prescription drug is not generally recognized as safe and effective and thus is limited to use under an approved new drug application for bacteriostatic skin cleansing and for the control of an outbreak of gram-positive infection where other infection control procedures have been unsuccessful. The physician is to be warned against use of hexachlorophene on burned, or denuded skin or on mucous membranes, or in routine prophylactic total body bathing and advised that hexachlorophene should be rinsed thoroughly after use. When, in a physician's judgment, a staphylococcal infection outbreak warrants the institution of measures beyond routine infection control practices, he may prescribe hexachlorophene, in the light of the warnings and precautions defined in the labeling. This use should generally be limited to short-term use and precludes routine prophylactic total body bathing.

To implement these conclusions and to protect adequately the public health, the Commissioner determines that the following procedures shall apply to outstanding stocks of products containing hexachlorophene:

a. Powders labeled for infant use containing above 0.75 percent hexachlorophene shall be recalled by the manufacturer. Baby powders are of particular concern because they are not rinsed off, are repeatedly applied, and are covered by diapers.

b. Those products other than powders labeled for infant use containing above 0.75 percent hexachlorophene in retail pharmacies shall immediately be removed from customer shelves to the prescription drug area of the pharmacy and shall be limited to distribution on a prescription of a physician. In medical institutions hexachlorophene products shall be restricted to prescription use. Such products in the hands of grocery stores or other nonprofessional outlets where there is no pharmacy shall be recalled by the manufacturer and may be relabeled as prescription drugs, if suitable.

c. The existing supplies of those products including those powders labeled for infant use, containing 0.75 percent or less hexachlorophene, need not be recalled by the manufacturer. These preparations are primarily soaps which are intended to be washed off. It is concluded that the public health is protected adequately by measures to control further production and shipment. Existing stocks in stores may be utilized. There is no data showing that the continued use of the limited stocks of such products presents a health hazard. Cessation of production and shipment is directed as a matter of prudence and sound medical caution pending the availability of further safety data. Production and shipment shall cease immediately upon publication of this order in the FEDERAL REGISTER (9–27–72).

d. Manufacturers of those products which are the subject of approved NDA's shall supplement their applications in accord with the requirements of this statement, to provide for reformulation and/or relabeling as necessary. Action to withdraw approval of new drug applications will be initiated if supplements have not been received within the time limits provided in this statement.

e. The Food and Drug Administration will contact professional societies and trade associations to help implement this policy by disseminating this information.

Accordingly, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(n), 502 (a), (f), (j) 503(b), 505, 601(a), 602(a), (c), 701(a), 52 Stat. 1041, 1050–55 as amended; 21 U.S.C. 321(n), 352 (a), (f), (j), 353(b), 355, 361(a), 362 (a), (c), 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120), the following new section is added to Part 3:

§ 3.91 Hexachlorophene, as a component of drug and cosmetic products.

(a) *Antibacterial component.* The use of hexachlorophene as an antibacterial component in drug and cosmetic products has expanded widely in recent years. It is used in such products because of its bacteriostatic action against gram-positive organisms, especially against strains of staphylococcus; however, hexachlorophene offers no protection against gram-negative infections. In addition the antibacterial activity depends largely on repeated use. A notice published in the FEDERAL REGISTER of April 4, 1972 (37 F.R. 6775), invited data on OTC antimicrobial ingredients, including hexachlorophene, for review by an OTC Drug Advisory Review Panel to be convened under the procedures set forth in the FEDERAL REGISTER of May 11, 1972 (37 F.R. 9464). This statement of policy will remain in effect unless and until replaced by a monograph resulting from the OTC Drug Advisory Review Panel.

(b) *Adverse effects.* Though considered safe for many years, recent information has become available associating hexachlorophene with toxic effects, including deaths. Studies have shown that toxic amounts of hexachlorophene can be absorbed through the skin of humans, especially the skin of premature babies or damaged skin. Human toxicity reports include data on symptomatology, blood and tissue levels of hexachlorophene, and descriptions of neuropathologic lesions. Recent infant deaths due to use of baby powder accidentally contaminated with 6 percent hexachlorophene have occurred. The accumulated evidence of toxicity is sufficient to require that continued marketing of hexachlorophene containing products be carefully defined in order to protect consumers.

(c) *Prescription drugs.* (1) Because of their potential for harmful effect, drugs containing hexachlorophene, other than as a preservative as described below, are not considered to have been shown to be safe and effective, are regarded as new drugs requiring approved new drug applications, and would be misbranded for over-the-counter distribution. In the interest of public health protection, hexachlorophene containing drugs will be regarded as misbranded and subject to regulatory proceedings unless the label bears the legend "Caution: Federal law prohibits dispensing without a prescription," and the labeling on or within the package from which the drug is to be dispensed bears adequate information for its safe and effective use by practitioners, in accord with § 1.106(b)(3 of this chapter.

(2) The Food and Drug Administration recognizes that hexachlorophene is useful as a bacteriostatic skin cleanser. It further concludes that the margin of safety is such that products containing hexachlorophene may appropriately be used within clearly delineated conditions of use.

(3) In order for such drugs to bear adequate information for safe and effective use the following statements are representative of the type of labeling for products shown to be effective bacteriostatic skin cleansers. Labeling for products other than bacteriostatic skin cleansers will be determinted through the new drug procedures based on the available data.

(i) In the labeling other than on the immediate container label.

INDICATIONS

1. Bacteriostatic skin cleanser for surgical scrubbing or handwashing as part of patient care.

2. For topical application to control an outbreak of gram-positive infection where other infection control procedures have been unsuccessful. Use only as long as necessary for infection control.

CONTRAINDICATIONS

1. Not for use on burned or denuded skin or on mucous membranes.

2. Not for routine prophylactic total body bathing.

WARNINGS

Rinse thoroughly after use. Patients should be closely monitored and use should be immediately discontinued at the first sign of any of the symptoms described below.

Hexachlorophene is rapidly absorbed and may produce toxic blood levels when applied to skin lesions such as ichthyosis congenita or the dermatitis of Letterer-Siwe's syndrome or other generalized dermatologic conditions. Application to burns has also produced neurotoxicity and death.

Infants have developed dermatitis, irritability, generalized clonic muscular contractions and decerebrate rigidity following application of a 6 percent hexachlorophene powder. Examination of brainstems of those infants revealed vacuolization like that which can be produced in newborn experimental animals following repeated topical application of 3 percent hexachlorophene. Moreover, a study of histologic sections of premature infants who died of unrelated causes has shown a positive correlation between hexachlorophene baths and lesions in white matter of brains.

(ii) On the immediate container label prominently displayed and in bold print:

"Special Warning: This compound may be toxic if used other than as directed. Rinse thoroughly after use. Monitor patients closely for toxicity symptoms."

(4) Marketing of products for the indications listed in subparagraph (3) of this paragraph may be continued if all the following conditions are met after the effective date of this section (9–27–72):

(i) The product is labeled with the prescription legend and adequate information for safe and effective use as set forth in subparagraph (3) of this paragraph.

(ii) Within 30 days, or by (10–27–72) the holder of an approved new drug application submits a supplement to provide for the revised label and full disclosure labeling. As the label and labeling will have been put into use, the supplement should be submitted under the provision of § 130.9(d) of this chapter.

(iii) Within 30 days, or by (10–27–72) the holder of an approved new drug application submits a supplement to provide for a revised formulation where appropriate to comply with this order.

(iv) Within 90 days, or by (12–26–72) the holder of an approved new drug application submits a supplement containing blood level data obtained from use of the drug as recommended, unless such information is a part of the new drug application file.

(v) Within 90 days, or by (12–26–72), the manufacturer or distributor of such a drug for which a new drug approval is not in effect submits a new drug application in accord with § 130.4 of the new drug regulations (21 CFR 130.4), including blood level data obtained from use of the drug as recommended.

(5) Prescription drug products may contain hexachlorophene as part of an effective preservative system under the conditions and limitations as provided for under paragraph (d) of this section.

(d) *Over-the-counter (OTC) drugs.* Over-the-counter drug products may contain hexachlorophene only as part of an effective preservative system, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available. This use of hexachlorophene will not, by itself, require an approved new drug application. Use of hexachlorophene as a preservative at a level higher than 0.1 percent is regarded as a new drug use requiring an approved new drug application, which must be submitted within the time set out in paragraph (c)(4) of this section.

(e) *Cosmetics.* Hexachlorophene may be used as a preservative in cosmetic products, at a level that is no higher than necessary to achieve the intended preservative function, and in no event higher than 0.1 percent. Such use of hexachlorophene shall be limited to situations where an alternative preservative has not yet been shown to be as effective or where adequate integrity and stability data for the reformulated product are not yet available. The component of a preservative system, whether hexachlorophene or other antimicrobial agent, should be selected on the basis of the effect on the total microbial ecology of the product, not merely on gram-positive bacteria.

(1) Adequate safety data do not presently exist to justify wider use of hexachlorophene in cosmetics.

(2) Antibacterial ingredients used as substitutes for hexachlorophene in cosmetic products, and finished cosmetic products containing such ingredients, shall be adequately tested for safety prior to marketing. Any such ingredient or product whose safety is not adequately substantiated prior to marketing may be adulterated and will in any event be deemed misbranded unless it contains a conspicuous front panel statement that the product has not been adequately tested for safety and may be hazardous.

(f) *Content statement.* All reference to hexachlorophene limit in this order is on a weight-in-weight (w/w) basis. Quantitative declaration of hexachlorophene content on the labeling of products, where required, shall be on a w/w basis. For aerosol products, the declaration will be independent of the propellent.

(g) *Shipments of products.* Shipments of products falling within the scope of paragraph (c), (d), or (e) of this section which are not in compliance with the guidelines stated herein shall be the subject of regulatory proceedings after the effective date of the final order.

(h) *Prior notices.* This order preempts any conditions for marketing products set forth in the following prior notices.

1. DESI No. 4749 (34 F.R. 15389, October 2, 1969), "Certain OTC Drugs for Topical Use."

2. DESI No. 2855 (35 F.R. 12423, August 4, 1970), "Certain Mouthwash and Gargle Preparations."

3. DESI No. 8940 (36 F.R. 14510, August 6, 1971), "Topical Cream Containing Pyrilamine Maleate, Benzocaine, Hexachlorophene, and Cetrimonium Bromide."

4. DESI No. 6615 (36 F.R. 18022, September 8, 1971), "Deodorant/Antiperspirant."

5. DESI No. 6270 (36 F.R. 23330, December 8, 1971), "Certain Preparations Containing Hexachlorophene".

(h) *Effective date.* This order will become effective upon publication in the FEDERAL REGISTER (9–27–72).

(Secs. 201(n), 502 (a), (f), (j), 503(b), 505, 601(a), 602 (a), (c), 701(a), 52 Stat. 1041, 1050–55 as amended; 21 U.S.C. 321(n), 352 (a), (f), (j), 353(b), 355, 361(a), 362 (a), (c), 371(a))

Dated: September 21, 1972.

CHARLES C. EDWARDS,
Commissioner of Food and Drugs.

[FR Doc.72–16442 Filed 9–26–72;8:50 am]

SUBCHAPTER C—DRUGS

PART 135a—NEW ANIMAL DRUGS FOR OPHTHALMIC AND TOPICAL USE

Kanamycin Sulfate, Calcium Amphomycin, and Hydrocortisone Acetate

The Commissioner of Food and Drugs has evaluated a new animal drug application (47–997V) filed by Bristol Laboratories, Division of Bristol-Myers Co., Post Office Box 657, Syracuse, N.Y. 13201, proposing the safe and effective use of kanamycin sulfate, calcium amphomycin, and hydrocortisone acetate cream for the treatment of dogs. The application is approved.

Therefore, pursuant to provisions of 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 (21 CFR 2.120), § 135a.8 *Kanamycin sulfate, calcium amphomycin, and hydrocortisone acetate* is amended by adding the words "or cream" between the word "ointment" and the word "base", and between the word "ointment" and the word "contains" in paragraph (a)(3).

Effective date. This order shall be effective upon publication in the FEDERAL REGISTER (9–27–72).

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

Dated: September 19, 1972.

C. D. VAN HOUWELING,
Director, Bureau of Veterinary Medicine.

[FR Doc.72–16387 Filed 9–26–72;8:45 am]

Title 50—WILDLIFE AND FISHERIES

Chapter I—Bureau of Sport Fisheries and Wildlife, Fish and Wildlife Service, Department of the Interior

PART 32—HUNTING

Certain National Wildlife Refuges in Montana; Correction

In F.R. (Doc. 14435), Volume 37, Number 166, dated Friday, August 25, 1972, on page 17176, § 32.22 *Special regulations; upland game; for individual wildlife refuge areas,* the Special Condition under Bowdoin National Wildlife Refuge should be amended to read as follows:

Special condition. Upland game hunting permitted during period pheasant season is open.

JOHN D. FINDLAY,
Regional Director, Bureau of Sport Fisheries and Wildlife.

SEPTEMBER 20, 1972.

[FR Doc.72–16407 Filed 9–26–72;8:47 am]