(a) Nutrition labeling in accordance with § 101.9.

* * * * *

(2) * * *

(iii) * * *

(a) Nutrition labeling in accordance with § 101.9.

* * * * *

(3) * * *

(ii) * * *

(a) Nutrition labeling in accordance with § 101.9.

* * * * *

b. Section 101.9 is amended by revising paragraphs (a)(2) and (h)(1)(i) and (2) to read as follows:

§ 101.9 Nutrition labeling of food.

(a) * * *

(2) If any vitamin and/or mineral is added to a food so that a single serving provides 50 percent or more of the U.S. Recommended Daily Allowance (U.S. RDA) for adults and children 4 years or more of age, as specified in paragraph (c)(7)(iv) of this section, of any one of the added vitamins and/or minerals, unless such addition is permitted or required in other regulations, e.g., a standard of identity or nutritional quality guideline, or is otherwise exempted by the Commissioner, the food shall be considered a food for special dietary use within the meaning of § 105.3(a)(1)(iii) of this section.

* * * * *

(h) * * *

(1)(i) Except where expressly covered by § 105.65 of this chapter, infant, baby, and junior-type food promoted for infants and children under 4 years of age shall include nutrition information on the label and in labeling in compliance with this section.

* * * * *

(2) Dietary supplements are exempted, except that the labeling of a dietary supplement in food form, e.g., a breakfast cereal, shall conform to the labeling established in paragraph (c) of this section, including the order for listing vitamins and minerals established in paragraph (c)(7)(iv) of this section.

PARTS 105—FOODS FOR SPECIAL DIETARY USE

2. In Part 105:

a. Section 105.3 is amended by revising paragraph (a)(1), by deleting paragraphs (b) and (c), by revising paragraphs (d) and (e), and by deleting paragraphs (f) and (g) as follows:

§ 105.3 Definitions and interpretations.

* * * * *

(a)(1) The term "special dietary uses", as applied to food for man, means particular (as distinguished from general) uses of food, as follows:

(i) Uses for supplying particular dietary needs which exist by reason of a physical, physiological, pathological or other condition, including but not limited to the conditions of diseases, convalescence, pregnancy, lactation, allergic hypersensitivity to food, underweight, and overweight;

(ii) Uses for supplying particular dietary needs which exist by reason of age, including but not limited to the ages of infancy and childhood;

(iii) Uses for supplementing or fortifying the ordinary or usual diet with any vitamin, mineral, or other dietary property. Any such particular use of a food is a special dietary use, regardless of whether such food also purports to be or is represented for general use.

* * * * *

(b) and (c) [Reserved]

(d) If a food purports to be or is represented for special dietary use by man by reason of the presence of any constituent which is not utilized in normal metabolism, the label shall bear a statement of the percent by weight of such constituent, and, in juxtaposition with the name of such constituent, the word "nonnutritive". If such constituent is fibrous plant matter, it shall be considered to be crude fiber and its percent expressed as such. But if such constituent is saccharin or a saccharin salt, the label shall bear, in lieu of such statement and word, the statement "Contains saccharin (or saccharin salt, as the case may be), a nonnutritive, artifical sweetener which should be used only by persons who must restrict their intake of ordinary sweets," the blank to be filled in with the percent by weight of saccharin or saccharin salt in such food. The provisions of this section shall not be construed as authorizing the use of saccharin or its salts in any food other than one for use by persons who must restrict their intake of carbohydrates, or as relieving any food from compliance with any requirement of section 402(b) or (d), 403(g), or other provisions of the act.

(e) For the purposes of the regulations in this part, the terms "infant," "child," and "adult" mean persons not more than 12 months old, more than 12 months but less than 12 years old, and 12 years or more old, respectively.

§§ 105.60, 105.77, and 105.85 [Revoked]

b. By revoking § 105.60 *Restrictions, placement, false or misleading respresentations,* § 105.77 *Vitamins and minerals,* and § 105.85 *Dietary supplements of vitamins and minerals.*

PART 201—LABELING

§ 201.19 [Amended]

3. In Part 201, § 201.19 is amended by changing "§ 105.3(d)" to read "§ 105.3(e)."

Because this order is a ministerial act revoking regulations already ruled by the Court of Appeals to be invalid, and because it relieves a restriction and there is no useful purpose in postponing the effective date, the Commissioner concludes, under the Administrative Procedure Act (5 U.S.C. 553(b)(B) and (d)(1) and (3)), that notice and public procedure and delayed effective date are unnecessary.

Executive Order 12044 on improving government regulations requires the agency to consider economic impacts in the development of regulations. Because this action is being taken to revoke regulations which the Court of Appeals has already invalidated, no assessment of its economic impact is being made at this time. No economic impacts are expected to occur from the revocation since no new requirements are imposed at this time. The economic impact of vitamin and mineral supplement standards and labeling regulations will be evaluated in the course of reissuing these regulations through the normal rulemaking procedure.

Effective date. This order is effective March 15, 1979.

Dated: March 12, 1979.

JOSEPH P. HILE,
Associate Commissioner for Regulatory Affairs.

[FR Doc. 79-7982 Filed 3-15-79; 8:45 am]

[4110-03-M]

Subchapter D—Drugs for Human Use

[Docket No. 78N-0341]

PART 448—PEPTIDE ANTIBIOTIC DRUGS

Combination Otic Solutions and Suspensions; Postponement of Effective Date

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This document postpones the effective date of a final rule that revises provisions for certification or release of certain combination otic products. The effective date is postponed to allow time for completion of review of the requests for a hearing.

DATE: Postponement is effective March 12, 1979.

FOR FURTHER INFORMATION CONTACT:

Nathan J. Treinish, Bureau of Drugs (HFD-32), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-3650.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of January 30, 1979 (44 FR 5879), the Director of the Bureau of Drugs promulgated a final rule to be effective on March 12, 1979, amending Part 448 of the antibiotic regulations (21 CFR Part 448) by revising § 448.430 (21 CFR 448.430) which provides for certification of polymyxin-B sulfate otic solution.

Hearing requests were received from two firms. In response to the January 30, 1979 final rule, Lemmon Pharmacal Co. filed a hearing request concerning Otocort (NDA 60-730). Kleinfeld, Kaplan and Becker, as attorneys for Burroughs Wellcome Co., filed a hearing request concerning Aerosporin Otic Solution (NDA 60-756, DESI 8426) and Lidosporin Otic Solution (NDA 50-171, DESI 50171).

Any data, information, and analyses on which the firms rely to justify a hearing must be submitted by April 2, 1979. The hearing requests will be reviewed, and when the review is completed the Commissioner of Food and Drugs will announce in the FEDERAL REGISTER whether or not Lemmon or Burroughs Wellcome has demonstrated the existence of a genuine and substantial issue of fact requiring a hearing.

A certification regulation exists for Aerosporin but not for Lidosporin or Otocort. Lidosporin and Otocort have been released pending a final determination as to their effectiveness.

Therefore, the effective date of the January 30, 1979 regulation as it pertains to the revision of § 448.430 is hereby postponed to allow time for completion of review of the hearing request for the product covered by this monograph, Aerosporin Otic Solution. In regard to the other two products, which are released, the date for ceasing to release the products is hereby postponed to allow time for completion of review of the hearing requests. If the result at the completion of this proceeding so indicates, monographs will be prepared to cover these released products.

The January 30, 1979 notice also amended 21 CFR Parts 444, 449, and 455. Because no person filed objections or a request for hearing concerning those parts, they are not affected by this notice, and the March 12, 1979 effective date is hereby confirmed.

This action is taken under the Federal Food, Drug, and Cosmetic Act (secs. 502, 507, 52 Stat. 1050-1051 as amended, 59 Stat. 463 as amended (21 U.S.C. 352, 357)) and under authority delegated to the Commissioner (21 CFR 5.1) and redelegated to the Director, Bureau of Drugs (21 CFR 5.78).

Effective date. This postponement is effective March 12, 1979.

(Secs. 502, 507, 52 Stat. 1050-1051 as amended, 59 Stat. 463 as amended (21 U.S.C. 352, 357))

Dated: March 9, 1979.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc. 79-7970 Filed 3-15-79; 8:45 am]

[4110-03-M]

SUBCHAPTER E—ANIMAL DRUGS, FEEDS, AND RELATED PRODUCTS

[Docket No. 77N-0164]

PART 514—NEW ANIMAL DRUG APPLICATIONS

Criteria for Adequate and Well-Controlled Investigations

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: This document updates the new animal drug regulations to provide for the use of untreated and individual controls as an alternate basis to establish the effectiveness of new animal drugs. As amended, the regulations more closely conform to those for human drugs.

EFFECTIVE DATE: April 16, 1979.

FOR FURTHER INFORMATION CONTACT:

Myron C. Rosenberg, Bureau of Veterinary Medicine (HFV-100), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, MD 20857, 301-443-5247.

SUPPLEMENTARY INFORMATION: In the FEDERAL REGISTER of September 20, 1977 (42 FR 47218) the Food and Drug Administration proposed to update the new animal drug regulations to provide for the use of untreated controls as an alternate basis to establish the effectiveness of new animal drugs. The proposed amendment to the regulations would make § 514.111 (21 CFR 514.111) more equivalent to the corresponding § 314.111 (21 CFR 314.111) covering drugs for human use. Interested persons were given 60 days to comment.

Two responses to the proposal were received. Comments were received from the Animal Health Institute (a national association representing producers of animal health and nutrition products) and a manufacturer of drug products intended for veterinary use. Both responses concurred with the proposed amendment to § 514.111, and both suggested a further modification to § 514.111(a)(4) to add a fifth method for comparing the results of treatment or diagnosis with a control so as to permit quantitative evaluation. The suggested fifth method was individual control. The responses maintained that in some cases an animal may serve as its own control and the results obtained before or during treatment may be used for comparison with those obtained in the same animal at the completion of therapy or necropsy. Examples were given of the importance of individual control, e.g., evaluating anthelmintics.

The Commissioner of Food and Drugs has evaluated the comments received and available information regarding "individual control" and concludes that a change in the regulation suggested in the comments received should be adopted but does not agree that this is a fifth method of control. The Commissioner concludes, rather, that it is an established principle that with an appropriate design the same animal can be used for both the test drug and control using three of the four types of proposed controls. This clarification has been added to the statement of principles of adequate and well-controlled clinical (field) investigations and is being finalized as proposed with the revised statement.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 512, 701(a), 52 Stat. 1055, 82 Stat. 343-351 (21 U.S.C. 360b, 371(a))) and under authority delegated to the Commissioner (21 CFR 5.1), Part 514 is amended in § 514.111 by revising paragraph (a) (3), (4), and (5) to read as follows:

§ 514.111 Refusal to approve an application.

(a) * * *

(3) The methods used in and the facilities and controls used for the manufacture, processing, and packing of such drug are inadequate to preserve its identity, strength, quality, and purity; or

(4) Upon the basis of the information submitted to the Food and Drug Administration as part of the application, or upon the basis of any other information before it with respect to such drug, it has insufficient information to determine whether such drug is safe for use under such conditions. In making this determination the Commissioner shall consider, among other relevant factors:

(i) The probable consumption of such drug and of any substance formed in or on food because of the use of such drug;

(ii) The cumulative effect on man or animal of such drug, taking into account any chemically or pharmacologically related substances;

(iii) Safety factors which, in the opinion of experts qualified by scientific training and experience to evaluate the safety of such drugs, are appropriate for the use of animal experimentation data; and

(iv) Whether the conditions of use prescribed, recommended, or suggested in the proposed labeling are reasonably certain to be followed in practice; or

(5) (i) Evaluated on the basis of information submitted as part of the application and any other information before the Food and Drug Administration with respect to such drug, there is lack of substantial evidence consisting of adquate and well-controlled investigations, including clinical (field) investigation, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could fairly and reasonably be concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the proposed labeling.

(ii) The following principles have been developed over a period of years and are recognized by the scientific community as the essentials of adequate and well-controlled clinical (field) investigations. They provide the basis for the determination whether there is "substantial evidence" to support the claims of effectiveness for "new animal drugs."

(*a*) The plan or protocol for the study and the report of the results of the effectiveness study must include the following:

(*1*) A clear statement of the objectives of the study.

(*2*) A method of selection of the subjects that—

(*i*) Provides adequate assurance that they are suitable for the purposes of the study, diagnostic criteria of the condition to be treated or diagnosed, confirmatory laboratory tests where appropriate, and, in the case of prophylactic agents, evidence of susceptibility and exposure to the condition against which prophylaxis is desired;

(*ii*) Assigns the subjects to test groups in such a way as to minimize bias; and

(*iii*) Assures comparability in test and control groups of pertinent variables, such as species, age, sex, duration and severity of disease, management practices, and use of drugs other than those being studied. When the effect of such variables is accounted for by an appropriate design, and when, within the same animal, effects due to the test drug can be obtained free of the effects of such variables, the same animal may be used for both the test drug and the control using the controls set forth in paragraph (a)(5)(ii)(*a*)(*4*)(*i*), (*ii*), or (*iii*) of this section.

(*3*) An explanation of the methods of observation and recording of the animal response variable studied and the means of excluding bias or minimizing bias in the observations.

(*4*) A comparison of the results of treatment or diagnosis with a control in such a fashion as to permit quantitative evaluation. The precise nature of the control must be stated and an explanation given of the methods used to minimize bias on the part of the observers and the analysts of the data. Level and methods of "blinding," if used, are to be documented. Generally, four types of comparisons are recognized:

(*i*) No treatment: Where objective measurements of effectiveness are available and placebo effect is negligible, comparison of the objective results in comparable groups of treated and untreated animals.

(*ii*) Placebo control: Comparison of the results of use of the new animal drug entity with an inactive preparation designed to resemble the test drug as far as possible.

(*iii*) Active treatment control: An effective regimen of therapy may be used for comparison, e.g., where the condition treated is such that no treatment or administration of a placebo would be contrary to the well-being of the animals.

(*iv*) Historical control: In some circumstances involving diseases with high and predictable mortality (leukemia or tetanus) or with signs and symptoms of predictable duration or severity (some forms of parasitism, bovine hypocalcemia, canine eclampsia) or in the case of prohylaxis where morbidity is predictable, the results of use of a new animal drug entity may be compared quantitatively with prior experience historically derived from the adequately documented natural history of the disease or condition in comparable animals with no treatments or with a regimen (therapeutic, diagnostic, prophylactic) whose effectiveness is established.

(*5*) A summary of the methods of analysis and an evaluation of data derived from the study, including any appropriate statistical methods.

(*6*) Any of the criteria in this paragraph (a)(5)(ii) may be waived in whole or in part, either before the investigation or in the evaluation of a completed study, by the Director of the Bureau of Veterinary Medicine with respect to a specific clinical (field) investigation. A petition for such a waiver may be filed by any person who would be adversely affected by application of the criteria to a particular clinical investigation. The petition should show that some or all of the criteria are not reasonably applicable to the investigation and that alternative procedures can be or have been followed, the results of which will yield or have yielded data that can and should be accepted as substantial evidence of the drug's effectiveness. A petition for a waiver shall set forth clearly and concisely the specific provision or provisions in the criteria from which waiver is sought, why the criteria are not reasonably applicable to the particular clinical (field) investigation, what alternative procedures, if any, are to be or have been employed, what results have been obtained, and the basis on which it can be or has been concluded that the clinical (field) investigation will yield or has yielded substantial evidence of effectiveness, notwithstanding nonconformance with the criteria for which waiver is requested.

(*b*) Standardized test drug: For such an investigation to be considered adequate for consideration for approval of a new animal drug, the test drug must be standardized as to identity, strength, quality, purity, and dosage form to give significance to the results of the investigation.

(*c*) Uncontrolled studies or partially controlled studies are not acceptable as the sole basis for the approval of claims of effectiveness. Such studies, carefully conducted and documented, may provide corroborative support of well-controlled studies regarding efficacy and may yield valuable data regarding safety of the test drug. Such studies will be considered on their merits in the light of the principles listed here, with the exception of the requirement for the comparison of the treated subjects with controls. Isolated case reports, random experience, and reports lacking the details which permit scientific evaluation will not be considered.

* * * * *

Effective date. This regulation becomes effective on April 16, 1979.

(Secs. 512, 701(a), 52 Stat. 1055, 82 Stat. 343-351 (21 U.S.C. 360b, 371(a)))

Dated: March 6, 1979.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 79-7643 Filed 3-15-79; 8:45 am]