

4. In § 2531.2 the words "manager of the land office for the district in which the land is situated" are changed to read "authorized officer."

5. Section 2531.3 is revised to read as follows:

§ 2531.3 Effect of application.

(a) Where an allotment application under the fourth section of the Act of February 8, 1887, as amended, 25 U.S.C. 334 (is not accompanied by the requisite certification from the Bureau of Indian Affairs showing the applicant to be eligible for an allotment, and the applicant is given time to furnish such certificate, the application does not segregate the land, and other applications therefor may be received and held to await final action on the allotment application.

(b) Where an allotment application is approved by the authorized officer, it operates as a segregation of the land, and subsequent application for the same land will be rejected.

[FR Doc.72-18458 Filed 10-30-72; 8:45 am]

Title 45—PUBLIC WELFARE

Chapter VII—Commission on Civil Rights

PART 701—ORGANIZATION AND FUNCTIONS OF THE COMMISSION

Miscellaneous Amendments

Section 701.1 of Part 701 is amended by deleting the word "and" following immediately after "(1967)" and substituting therefor a comma; the section is also amended by deleting the period following immediately after "(1970)" and substituting therefor the following: "and by 86 Stat. 813 (1972)."

Subparagraphs (1) and (4) of paragraph (a) of § 701.2 of Part 701 are each amended by inserting immediately after "religion," the following: "sex,"

Paragraph (b) of § 701.2 of Part 701 is amended by deleting "January 31, 1973" and substituting therefor the following: "the last day of fiscal year 1978".

Section 702.15 of Part 702 is amended by deleting the following:

Pursuant to section 102(j) of the Act: A witness attending any session of the Commission shall receive \$6 for each day's attendance and for the time necessarily occupied in going to and returning from the same, and 10 cents per mile for going from and returning to his place of residence; witnesses who attend at points so far removed from their respective residences as to prohibit return thereto from day to day shall be entitled to an additional allowance of \$10 per day for expenses of subsistence, including the time necessarily occupied in going to and returning from the place of attendance; and,

and by substituting the following:

Pursuant to section 102(j) of the Act: A witness attending any session of the Commission shall be paid the same fees and mileage that are paid witnesses in the courts of the United States.

The section is amended further by capitalizing the word "Mileage".

Paragraph (a) of § 703.2 of Part 703 is amended by inserting immediately after "religion," the following: "sex,"

These amendments shall become effective on the date of their publication in the FEDERAL REGISTER.

THEODORE M. HESBURGH,
Chairman.

[FR Doc.72-18550 Filed 10-30-72; 8:48 am]

Title 49—TRANSPORTATION

Chapter X—Interstate Commerce Commission

SUBCHAPTER D—TARIFFS AND SCHEDULES
[Docket No. 35613]

PART 1309—TARIFFS AND CLASSIFICATIONS OF FREIGHT FORWARDERS

Transmission of Tariffs and Schedules to Subscribers and Other Interested Parties

Correction

In F.R. Doc. 72-15672 appearing at page 18550 of the issue for Wednesday, September 13, 1972, in § 1309.5(a)(1), the following material should be inserted after the word "Service," in the penultimate line of the certification: "etc. If the U.S. Postal Service,".

Title 21—FOOD AND DRUGS

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

SUBCHAPTER C—DRUGS

PART 130—NEW DRUGS

Subpart A—Procedural and Interpretive Regulations

APPLICABILITY OF DESI NOTICES AND NOTICES OF OPPORTUNITY FOR HEARING TO IDENTICAL, RELATED, AND SIMILAR DRUG PRODUCTS

In the FEDERAL REGISTER of February 10, 1972 (37 F.R. 2969), a notice was published proposing to delineate the applicability of Drug Efficacy Study Implementation Notices and Notices of Opportunity for Hearing to identical, related, and similar drug products. Interested persons were invited to submit comments on the proposal within 60 days. Comments were received from seven pharmaceutical manufacturers, three associations of pharmaceutical manufacturers, and one individual. The principal comments were as follows:

1. The most frequently occurring comment was that the definition of identical, related, or similar drugs is so broad that it is meaningless, and could result in drugs being subject to regulatory actions because of some vague unrecognized similarity to reviewed drugs. A further comment noted that the definition of identical, related, or similar

drugs is essentially the same as that which appears in 21 CFR 130.1(k) of the New Drug Regulations, and that this definition deals only with side effects and contraindications, and not with a relationship with respect to effectiveness. The Commissioner of Food and Drugs finds that it is in the public interest for conclusions of the Drug Efficacy Study to apply to all identical drug products, and to reasonably related and similar drug products. It is necessary that the definition be broad so that manufacturers are alerted to the possibility of their products being affected. The drug efficacy findings are clearly applicable to other brands of an identical drug. Other examples are equally clear, such as different salts of the same active moiety, or use of the same ingredient in a different combination. There will be, however, areas where the judgment of experts must determine the applicability of the efficacy findings. The determination will be based on the chemical structure of the drug, recommended use, route of administration, its pharmacological properties and any other information available on the action or properties of the drug.

The Commissioner recognizes that apparent slight differences in drugs such as a salt, an ester, an isomer, and others, may produce very different effects. This regulation is not intended to impute properties or lack of properties to a similar or related drug when there is evidence of different effects. The policy makes it incumbent on the sponsor of the drug to have data showing that his similar or related drug does in fact have different actions or effects. In the absence of such data it is reasonable to conclude that the drug efficacy conclusions are applicable. It is also clear that there will be instances in which the effectiveness evaluations on an oral dosage form will in no way apply to any other dosage form of the same drug. The Commissioner concludes that the principles involved in applying efficacy evaluations and adverse effect information to identical, similar, or related drug products are essentially the same, and it is therefore appropriate for the definition in this section to be essentially the same as that in § 130.1(k).

2. Several comments asked how a manufacturer could determine whether or not his drug product was related to a primary drug with a new drug application (NDA) approval that had become the subject of a drug efficacy notice. The Food and Drug Administration is actively engaged in attempting to identify all related drug products for which drug efficacy notices apply. If a manufacturer is not certain whether his product is covered by the new drug application subject to the notice he should request an opinion from the Bureau of Drugs of the FDA. The regulation has been clarified in this respect.

3. Several comments stated that the proposal ignored the basic distinction between old and new drugs and the protection of the grandfather clause. The Commissioner concludes that this view is without merit. Information as to a

drug's safety and effectiveness is applicable no matter what the status of the product is under the law. If a drug is found to lack substantial evidence of effectiveness for any of its claims and the manufacturer can establish that his product is exempted from the efficacy provisions by the grandfather provisions in the act, it is required that action be taken against that product through the misbranding procedures rather than under the new drug provisions. The FDA is still obligated to proceed against the product. The final order has been clarified to reflect this.

4. There was a comment that it was contrary to the Food and Drug Administration's recent policy statement on combination drug products to apply to such products containing an identical, related, or similar drug products, a notice relating to a single-drug product. The FDA believes that this policy is in full agreement with the combination policy. It is true that, in evaluating a combination preparation, the interaction or combined effect of two or more drugs must be taken into account. However, when an individual drug has been evaluated as less than effective, the inclusion of that drug, or a related or similar drug, in a combination preparation for the same indications for which it has been evaluated as less than effective, causes the drug efficacy evaluation to be applicable to the combination product. It cannot be presumed, in the absence of any conclusive data, that the interaction or combined effect of the two or more drugs will alter the less than effective evaluation of the individual drug.

5. One comment noted that the proposal does not exempt OTC preparations, and that they should be exempted since they are subject to a separate study. The FDA published as a proposal a clarification of the status of over-the-counter preparations reviewed in the Drug Efficacy Study in the FEDERAL REGISTER on April 20, 1972 (37 F.R. 7807). That proposal informed manufacturers that deferral for review by the OTC panels was not appropriate for OTC products for which evaluations were published and finalized, classifying these drugs as lacking either substantial evidence of effectiveness or as not shown to be safe. Other OTC products for which deferral of implementation was not considered appropriate were also listed in the same publication. Other than these specific OTC products, OTC products will not be the subject of drug efficacy implementation notices unless the FDA notifies manufacturers by public notice or letter. The FEDERAL REGISTER proposal of April 20, 1972, received no adverse comment and will be promulgated shortly. The OTC drug monographs published pursuant to the OTC panel reviews will indicate their applicability to similar or related drug products (see FEDERAL REGISTER order published May 11, 1972 (37 F.R. 9464)). A new paragraph (f) has been added to § 130.40 to clarify the effect of this order on OTC preparations.

6. Several comments objected to the burden the proposal would place on pur-

chasing agents when applying the same purchasing policy to identical, related, or similar drug products as to those named in the drug efficacy notices. This proposal does not place a significant burden on purchasing agents. In many instances a determination can readily be made by an individual who is familiar with drugs and their indications for use. Where the relationships are more subtle and not readily recognized except by experts, the purchasing agent may request an opinion from the FDA. The FDA maintains close liaison with purchasing agents of Federal agencies with major drug purchasing programs. To assure a clear procedure for obtaining an opinion by a purchasing agent, the final order is revised to include instructions on how to obtain such opinions.

7. Comments were received on paragraph (d) of the proposal, objecting to what was described as the FDA's encouraging of informers, and transferring its responsibilities to others. FDA presently has no means by which to readily determine what products are on the market that may be identical, related or similar to drugs subject to drug efficacy notices. In the interest of equitable application of the drug efficacy notices to all applicable products, the regulation provides a means for interested persons to bring to the FDA's attention related products. The FDA will then arrive at a decision based on scientific judgment as to the applicability of the drug efficacy notices to such products. This does not in any way transfer the FDA's responsibility to any other person.

8. Other comments argued that if less than effective drug efficacy notice conclusions apply to related products, then effective ratings should also apply. The Commissioner agrees that efficacy notices may be applied to a similar or related drug product provided that experts would conclude that the drug in question is sufficiently similar to the drug subject to the drug efficacy notices to justify a reasonable application of the efficacy conclusions. Present drug efficacy notices reflect this by requiring only abbreviated NDA's in many instances. It is possible that, with limited confirmatory testing, a related drug product may also be evaluated as safe and effective for its indications. Efficacy ratings do apply to identical drugs manufactured by a different firm; except that where questions of bioavailability between different formulations are present, evidence to establish bioavailability may be necessary. Until the safety and effectiveness of a drug become sufficiently recognized to justify an abbreviated NDA or no NDA, however, the law requires complete testing for each new drug.

9. There was comment that there is nothing in the act to authorize the FDA to extrapolate the findings of the Drug Efficacy Study to related products nor was such the intent of Congress. It is the opinion of the FDA that it was not the intent of Congress to restrict the Drug Efficacy Study to a study of drugs by "brand name" rather than by generic drug. There is nothing in the statute in-

dicating that identical, related or similar products should be handled differently depending upon who holds an NDA. Such an interpretation is contrary to the public interest and inconsistent with the concepts of justice and fair competition. It would result in a severe penalty to those products that had complied with the law and were cleared through the established new drug procedures, and would reward those products which were marketed without clearance.

10. One comment stated that "the Commissioner has no jurisdiction to adjudicate the effectiveness of a drug not covered by an NDA." The comment further stated that drug efficacy notices are proceedings under section 505(e) of the Food, Drug, and Cosmetic Act, and the effect of such withdrawal of approval extends only to the NDA under review, and is not binding on a product not subject to an NDA. The FDA's position is that an identical, similar, or related drug product is covered by the NDA for the basic product and thus is directly affected by a drug efficacy notice. Any required changes specified in the notice, therefore, apply to the identical, related, or similar drug product as appropriate; for example, requests for new drug applications, abbreviated new drug applications, bioavailability data, or labeling changes.

11. A comment stated that the ex post facto decision to apply the drug efficacy conclusions to "similar drugs" deprives the industry of due process of law, in that there was no duty imposed on industry to offer information on related drugs to the review panel, and no opportunity was afforded industry to do so. The comment further stated that the proponents of "similar drugs" were not parties to the regulatory hearings withdrawing approval of NDAs. The Commissioner concludes that the FDA has given manufacturers and distributors of identical, similar, or related drug products ample opportunity to submit data and be heard. The responsibility for determining whether a product is legally marketed rests with the sponsor. The FDA continues to take measures to notify drug manufacturers and distributors of drugs that may be affected by a Notice of Opportunity for Hearing. In the FEDERAL REGISTER notices announcing the results of the NAS-NRC and FDA evaluations of the drugs, the FDA has uniformly requested information from all manufacturers. The regulation has been revised to make this clear. In the case of drugs lacking substantial evidence of effectiveness past notices have stated that sponsors or any interested person who might be adversely affected by the removal of the drug from the market could submit data bearing on the proposal. No one in the regulated industry can now claim surprise on this matter.

12. There was comment that the FDA should list all products that it considers subject to a particular drug efficacy notice by name, dosage form, and strength, so that every manufacturer/distributor would know what products the FDA has concluded that the an-

nouncement covers. As was stated in the proposal, this is not feasible at this time. In the absence of a requirement in the law that all marketed drugs be listed with the FDA, the FDA does not have knowledge of every product that is on the market. Any list that could be compiled would be incomplete. The FDA does try to identify and notify those manufacturers or distributors of drugs found lacking substantial evidence of effectiveness, giving them the opportunity for voluntary compliance prior to initiating any legal action.

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 701(a), 52 Stat. 1050-1051 as amended, 1052-1053 as amended, 1055; 21 U.S.C. 352, 355, 371(a)) and the Administrative Procedure Act (5 U.S.C. 554) and under authority delegated to the Commissioner (21 CFR 2.120), Part 130 is amended by adding the following new section:

§ 130.40 Applicability of Drug Efficacy Study Implementation Notices and Notices of Opportunity for Hearing to identical, related, and similar drug products.

(a) The Food and Drug Administration's conclusions on the effectiveness of drugs are currently being published in the FEDERAL REGISTER as Drug Efficacy Study Implementation (DESI) Notices and as Notices of Opportunity for Hearing. The specific products listed in these notices include only those that were introduced into the market through the new-drug procedures from 1938-62 and are submitted for review by the National Academy of Sciences-National Research Council (NAS-NRC), Drug Efficacy Study Group. Many products which are identical to, related to, or similar to the products listed in these notices have been marketed under different names or by different firms during this same period or since 1962 without going through the new-drug procedures or the Academy review. Even though these products are not listed in the notices, they are covered by

the new drug applications reviewed and thus are subject to these notices. All persons with an interest in a product that is identical, related, or similar to a drug listed in a drug efficacy notice or a notice of opportunity for a hearing will be given the same opportunity as the applicant to submit data and information, to request a hearing, and to participate in any hearing. It is not feasible for the Food and Drug Administration to list all products which are covered by an NDA and thus subject to each notice. However, it is essential that the efficacy conclusions be applied to all identical, related, and similar drug products to which those conclusions are reasonably applicable. Any product not in compliance with an applicable drug efficacy notice is in violation of section 505 (new drugs) and/or section 502 (misbranding) of the act.

(b) An identical, related, or similar drug includes other brands, potencies, dosage forms, salts, and esters of the same drug moiety as well as of any drug moiety related in chemical structure or known pharmacological properties. Where experts qualified by scientific training and experience to evaluate the safety and effectiveness of drugs would conclude that the findings in a drug efficacy notice or notice of opportunity for hearing concerning effectiveness are applicable to an identical, related, or similar drug product, such product is affected by the notice. A combination drug product containing an identical, related, or similar drug is also subject to the conclusions contained in the notice. Any person may request an opinion on the applicability of such a notice to a specific product by writing to the Food and Drug Administration at the address shown in paragraph (e) of this section.

(c) Manufacturers and distributors of drugs should review their products as drug efficacy notices are published and assure that identical, related, or similar products comply with all the provisions of the notices.

(d) The published notices and summary lists of the conclusions are of par-

ticular interest to drug purchasing agents. These agents should take particular care to assure that the same purchasing policy applies to drug products that are identical, related, or similar to those named in the drug efficacy notices. The Food and Drug Administration applies the same regulatory policy to all such products. In many instances a determination can readily be made as to the applicability of a drug efficacy notice by an individual who is knowledgeable about drugs and their indications for use. Where the relationships are more subtle and not readily recognized, the purchasing agent may request an opinion by writing to the Food and Drug Administration at the address shown in paragraph (e) of this section.

(e) Interested parties may submit to the Food and Drug Administration, Bureau of Drugs, Office of Compliance, BD-300, 5600 Fishers Lane, Rockville, MD 20852, the names of drug products, and of their manufacturers or distributors, that should be the subject of the same purchasing and regulatory policies as those reviewed by the Drug Efficacy Study Group. Appropriate action, including referral to purchasing officials of various government agencies, will be taken.

(f) This regulation does not apply to OTC drugs identical, similar, or related to a drug in the Drug Efficacy Study unless there has been or is notification in the FEDERAL REGISTER that a drug will not be subject to an OTC panel review pursuant to § 130.301.

Effective date. This order shall be effective upon publication in the FEDERAL REGISTER (10-31-72).

(Secs. 502, 505, 701(a), 52 Stat. 1050-1051, as amended, 1052-1053, as amended, 1055, 21 U.S.C. 352, 355, 371(a); 5 U.S.C. 554)

Dated: October 27, 1972.

CHARLES C. EDWARDS,
Commissioner of
Food and Drugs.

[FR Doc.72-18654 Filed 10-30-72; 10:03 am]