



[DESI 13334]

**DEXAMETHASONE SODIUM PHOSPHATE AND LIDOCAINE HYDROCHLORIDE FOR PARENTERAL USE****Drugs for Human Use; Drug Efficacy Study Implementation**

The Food and Drug Administration has evaluated a report received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following steroid preparations for parenteral use:

Decadron Phosphate with Xyllocaine Injection and Decadron Phosphate with Xyllocaine Injection, Dilute, each containing dexamethasone sodium phosphate and lidocaine hydrochloride; Merck, Sharp & Dohme, Division of Merck & Co., Inc., West Point, Pa. 19486 (NDA 13-334).

The Food and Drug Administration has considered the Academy report, as well as other available evidence, and concludes that there is a lack of substantial evidence, within the meaning of the Federal Food, Drug, and Cosmetic Act, that these fixed combination drugs will have the effects that they purport or are represented to have under the conditions of use prescribed, recommended or suggested in the labeling.

Accordingly, the Commissioner of Food and Drugs intends to initiate proceedings to withdraw approval of the above listed new drug application.

Prior to initiating such action, however, the Commissioner invites the holder of the new-drug application for these drugs and any interested person who might be adversely affected by their removal from the market, to submit pertinent data bearing on the proposal within 30 days after publication hereof in the FEDERAL REGISTER. To be acceptable for consideration in support of the effectiveness of a drug, any such data must be previously unsubmitted, well-organized, and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in § 130.12(a) (5) of the regulations published as a final order in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for the approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

This announcement of the proposed action and implementation of the NAS-NRC report for these drugs is made to give notice to persons who might be adversely affected by their withdrawal from the market. From publication of an order withdrawing approval of the new-drug application will cause any such drug on the market to be a new drug for which an approved new-drug application is not in effect and will make it subject to regulatory action.

The above named holder of the new-drug application for these drugs has been mailed a copy of the NAS-NRC report. Any interested person may obtain a copy

of the report by writing to the office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 13334 and be directed to the attention of the appropriate office listed below and addressed to the Food and Drug Administration.

Requests for NAS-NRC reports: Press Relations Staff (OE-200), 200 O Street SW, Washington, D.C. 20204.

All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (BD-201), Bureau of Drugs, 5600 Fishers Lane, Rockville, Md. 20852.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: August 31, 1970.

SAM D. FINE,  
Associate Commissioner  
for Compliance.

[F.R. Doc. 70-12608; Filed, Sept. 22, 1970; 8:47 a.m.]

[DESI 6343]

[Docket No. FDC-D-235; NDA 6343 et al.]

**HYALURONIDASE****Drugs for Human Use; Drug Efficacy Study Implementation**

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following hyaluronidase drugs intended for injectable use in humans:

1. Wydase Solution and Wydase Lyophilized; marketed by Wyeth Laboratories, Inc., Post Office Box 8299, Philadelphia, Pa. 19101 (NDA 6-343).
2. Alidase; marketed by G. D. Searle & Co., Post Office Box 5110, Chicago, Ill. 60680 (NDA 6-714).
3. Hyazyme; marketed by Abbott Laboratories, North Chicago, Ill. 60064 (NDA 7-933).

The drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. A new drug application is required from any person marketing such drugs without approval.

The Food and Drug Administration is prepared to approve new drug applications and supplements to previously approved new drug applications under conditions described in this announcement.

**A. Effectiveness classification.** The Food and Drug Administration has considered the Academy reports, as well as other available evidence, and concludes that:

1. Hyaluronidase is effective for enhancing the dispersion and absorption of other injected drugs; for hypodermoclysis; as an adjunct in subcutaneous

urography; for improving resorption of radiopaque agents.

2. Hyaluronidase is probably effective as an aid in retrobulbar and cone injection infiltrative anesthesia in ocular surgery; for reducing painful swelling by absorption of locally accumulated fluid (transudates or blood) due to trauma; for hastening the onset of action and diffusibility of local anesthetics; in minimizing tumoraction during surgery; and for reducing postoperative edema and ecchymosis.

3. Hyaluronidase lacks substantial evidence of effectiveness for use in postoperative eye edema; for the resolution of early pterygiums; to hasten the reabsorption of traumatic subconjunctival hemorrhage and to dissolve the products of degenerative keratitis; and as an adjunct in producing hypotonia.

4. The drug is considered possibly effective for other labeled indications.

**B. Form of drug.** Hyaluronidase preparations are sterile solutions or powder for reconstitution and are suitable for injection.

**C. Labeling conditions.** 1. The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

2. The drug is labeled to comply with all requirements of the Act and regulations. Its labeling bears adequate information for safe and effective use of the drug and is in accord with the effectiveness classifications, the guidelines for uniform labeling published in the FEDERAL REGISTER of February 6, 1970, and, where applicable, the Academy's comments. The "Indications" section is as follows:

**INDICATIONS**

This drug is indicated as an adjuvant to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; as an adjunct in subcutaneous urography; for improving resorption of radiopaque agents; as an aid in retrobulbar and cone injection infiltrative anesthesia in ocular surgery; as an adjunct in reducing painful swelling by resorption of locally accumulated fluid; for hastening the onset of action and diffusibility of local anesthetics; for minimizing tumoraction during surgery and reducing postoperative edema and ecchymosis.

**D. Indications permitted during extended period for obtaining substantial evidence.** 1. Those indications for which the drug is described in paragraph A2 above as probably effective are included in the labeling conditions in paragraph C and may continue to be used for 12 months following the date of this publication to allow additional time within which holders of previously approved applications or persons marketing the drug without approval may obtain and submit to the Food and Drug Administration data to provide substantial evidence of effectiveness.

2. Those indications for which the drug is referenced in paragraph A4 above as possibly effective (not included in the labeling conditions in paragraph C) may continue to be used for 6 months following the date of this publication to allow additional time within which

holders of previously approved applications or persons marketing the drug without approval may obtain and submit to the Food and Drug Administration data to provide substantial evidence of effectiveness.

To be acceptable for consideration in support of the effectiveness of a drug, any such data must be previously unsubmitted, well-organized, and include data from adequate and well-controlled clinical investigations (identified for ready review) as described in § 130.12(a) (5) of the regulations published as a final order in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially controlled situations are not acceptable as a sole basis for the approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety.

**E. Marketing status.** Marketing of the drug may continue under the conditions described in paragraphs F and G of this announcement except that those indications referenced in paragraph D may continue to be used as described therein.

**F. Previously approved applications.** 1. Each holder of a "deemed approved" new drug application (i.e., and application which became effective on the basis of safety prior to Oct. 10, 1962) for such drug is requested to seek approval of the claims of effectiveness and bring the application into conformance by submitting supplements containing:

a. Revised labeling as needed to conform with the labeling conditions described herein for the drug, and complete current container labeling, unless recently submitted.

b. Updating information as needed to make the application current.

2. Such supplements should be submitted within the following time periods after the date of publication of this announcement in the FEDERAL REGISTER:

a. 60 days for revised labeling—the supplement should be submitted under the provisions of § 130.9 (d) and (e) of the new drug regulations (21 CFR 130.9) which permit certain changes to be put into effect at the earliest possible time.

b. 60 days for updating information.

3. Marketing of the drug may continue until the supplemental applications submitted in accord with the preceding subparagraphs 1 and 2 are acted upon, provided that within 60 days after the date of this publication, the labeling of this preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described in this announcement. (It may continue to include the indications referenced in paragraph D for the periods stated.)

**G. New applications.** 1. Any other person who distributes or intends to distribute such drug which is intended for the conditions of use for which it has been shown to be effective, as described under paragraph A above, should submit a new drug application containing full information required by the new drug application form FD-356H (21 CFR 130.4(c)). Such applications should in-

clude proposed labeling which is in accord with the labeling conditions described herein.

2. Distribution of any such preparation currently on the market without an approved new drug application may be continued provided that:

a. Within 60 days from the date of publication of this announcement in the FEDERAL REGISTER, the labeling of such preparation shipped within the jurisdiction of the Act is in accord with the labeling conditions described herein. (It may continue to include the indications referenced in paragraph D for the period stated.)

b. The manufacturer, packer, or distributor of such drug submits, within 180 days from the date of this publication, a new drug application to the Food and Drug Administration.

c. The applicant submits additional information that may be required for the approval of the application within a reasonable time as specified in a written communication from the Food and Drug Administration.

d. The application has not been ruled incomplete or unapprovable.

**H. Opportunity for a hearing.** 1. The Commissioner of Food and Drugs proposes to issue an order under the provisions of section 505(e) of the Federal Food, Drug, and Cosmetic Act withdrawing approval of all new-drug applications and all amendments and supplements thereto providing for the indications for which substantial evidence of effectiveness is lacking as described in paragraph A3 of this announcement. An order withdrawing approval of the applications will not issue if such applications are supplemented, in accord with this notice, to delete such indications. Promulgation of the proposed order would cause any drug for human use containing the same components and offered for the indications for which substantial evidence of effectiveness is lacking, to be a new drug for which an approved new-drug application is not in effect. Any such drug then on the market would be subject to regulatory proceedings.

2. In accordance with the provisions of section 505 of the Act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Part 130), the Commissioner will give the holders of any such applications, and any interested person who would be adversely affected by such an order, an opportunity for a hearing to show why such indications should not be deleted from labeling. A request for a hearing must be filed within 30 days after the date of publication of this notice in the FEDERAL REGISTER. A request for a hearing may not rest upon mere allegations or denials but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing, together with a well-organized and full-factual analysis of the clinical and other investigational data the objector is prepared to prove in a hearing. Any data submitted in response to this notice must be previously unsubmitted and include data from adequate and well-controlled clinical investiga-

tions (identified for ready review) as described in § 130.12(a) (5) of the regulations published in the FEDERAL REGISTER of May 8, 1970 (35 F.R. 7250). Carefully conducted and documented clinical studies obtained under uncontrolled or partially-controlled situations are not acceptable as a sole basis for approval of claims of effectiveness, but such studies may be considered on their merits for corroborative support of efficacy and evidence of safety. If a hearing is requested and is justified by the response to this notice, the issues will be defined, a hearing examiner will be named, and he shall issue a written notice of the time and place at which the hearing will commence.

A copy of the NAS-NRC report has been furnished to each firm referred to above. Any other interested person may obtain a copy by request to the appropriate office named below.

Communications forwarded in response to this announcement should be identified with the reference number DESI 6343 and be directed to the attention of the appropriate office listed below and addressed (unless otherwise specified) to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20852:

Supplements (Identify with NDA number): Office of Marketed Drugs (BD-200), Bureau of Drugs.

Original new drug applications: Office of New Drugs (BD-100), Bureau of Drugs.

Request for Hearing (Identify with Docket number): Hearing Clerk, Office of General Counsel (GC-1), Room 8-62, Parklawn.

All other communications regarding this announcement: Special Assistant for Drug Efficacy Study Implementation (BD-201), Bureau of Drugs.

Requests for NAS-NRC report: Press Relations Office (CE-200), Food and Drug Administration, 200 C Street SW., Washington, D.C. 20204.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-63, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: September 3, 1970.

SAM D. FINE,  
Associate Commissioner  
for Compliance.

[F.R. Doc. 70-12609; Filed, Sept. 22, 1970; 8:47 a.m.]

[DESI 6311]

**CERTAIN OXYTETRACYCLINE HYDROCHLORIDE, CHLORTETRACYCLINE HYDROCHLORIDE, TETRACYCLINE HYDROCHLORIDE, AND BACITRACIN PREPARATIONS FOR INHALATION, TOPICAL OR OTIC USE**

**Drugs for Human Use; Drug Efficacy Study Implementation**

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study

[DESI 4203]

**CERTAIN GAMMA BENZENE HEXACHLORIDE TOPICAL PREPARATIONS****Drugs for Human Use; Drug Efficacy Study Implementation Follow-Up Notice**

In a notice (DESI 4203) published in the *Federal Register* of September 17, 1970 (35 F.R. 14576), the Commissioner of Food and Drugs announced his conclusions pursuant to evaluation of reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on Kwell Shampoo (NDA 10-718) and Kwell Cream (NDA 6-309) containing gamma benzene hexachloride marketed by Reed and Carnrick, 30 Boright Avenue, Kenilworth, NJ 07033.

The notice stated that the shampoo was effective or probably effective for its labeled indications and the cream was effective or possibly effective for its labeled indications. The indications classified as probably effective and possibly effective have been reclassified as lacking substantial evidence of effectiveness in that no new evidence of effectiveness has been submitted pursuant to the September 17, 1970 notice.

The holder of the above-listed new drug applications has satisfactorily supplemented the applications to delete from the labeling all indications other than those regarded as effective. Other holders of applications approved for these drugs should submit within 60 days following publication of this notice in the *Federal Register*, supplements to their new drug applications to provide for revised labeling in accord with this notice. Such supplements should be submitted under the provisions of § 130.9 (d) and (e) of the new drug regulations (21 CFR 130.9 (d) and (e)) which permit certain changes to be put into effect at the earliest possible time.

Any such preparation, for human use, introduced into interstate commerce after 60 days following publication of this notice in the *Federal Register* with labeling bearing indications for which the drugs lack substantial evidence of effectiveness, may be subject to regulatory proceedings.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: June 13, 1972.

SAM D. FINE,  
Associate Commissioner  
for Compliance.

[FR Doc.72-3467 Filed 6-22-72;9:49 am]

[DESI 6343]

**HYALURONIDASE****Drugs for Human Use; Drug Efficacy Study Implementation Follow-Up Notice**

In a notice (DESI 6343) published in the *Federal Register* of September 23, 1970 (35 F.R. 14800), the Commissioner of Food and Drugs announced his conclusions pursuant to an evaluation of reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs containing hyaluronidase:

1. Wydase Solution and Wydase Lyophilized; Wyeth Laboratories, Inc., Post Office Box 8299, Philadelphia, Pa. 19101 (NDA 6-343).

2. Allidase; G. D. Searle & Co., Post Office Box 5110, Chicago, Ill. 60680 (NDA 6-714).

3. Hyazyme; Abbott Laboratories, North Chicago, Ill. 60064 (NDA 7-933).

The notice stated that the drugs were regarded as effective, probably effective, possibly effective, and lacking substantial evidence of effectiveness for their various labeled indications and allowed holders of the new drug applications, and persons marketing the drugs without approval, additional time to obtain and submit data to substantiate the claims classified as probably and possibly effective. Since no new evidence has been received, these drugs have been reclassified as lacking substantial evidence of effectiveness for labeled indications other than those appearing in the "Indications" section which follows:

**INDICATIONS**

Hyaluronidase is indicated as an adjunct to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; as an adjunct in subcutaneous urography for improving the resorption of radiopaque agents.

The new drug applications held by the firms listed above have been satisfactorily supplemented to delete those claims for which substantial evidence of effectiveness is lacking and to be in accord with the "Indications" section above.

The holders of applications approved for hyaluronidase should submit, within 60 days following publication of this amended announcement in the *Federal Register*, supplements to their new drug applications to provide for revised labeling in accord with the "Indications" section above. Such supplements should be submitted under the provisions of § 130.9 (d) and (e) of the new drug regulations (21 CFR 130.9 (d) and (e)) which permit certain changes to be put into effect at the earliest possible time.

Any such preparation, for human use, introduced into interstate commerce after 60 days following publication of this notice in the *Federal Register* with labeling bearing indications that lack substantial evidence of effectiveness may be subject to regulatory proceedings.

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat.

1050-53, as amended; 21 U.S.C. 352, 355) and under authority delegated to the Commissioner of Food and Drugs (21 CFR 2.120).

Dated: June 13, 1972.

SAM D. FINE,  
Associate Commissioner  
for Compliance.

[FR Doc.72-0468 Filed 6-23-72;9:40 am]

[DESI 8593]

**CERTAIN OPHTHALMIC/OTIC OINTMENTS****Drugs for Human Use; Drug Efficacy Study Implementation**

The Food and Drug Administration has evaluated reports received from the National Academy of Sciences-National Research Council, Drug Efficacy Study Group, on the following drugs for ophthalmic and/or otic use.

Terramycin Ophthalmic-Otic Ointment with Polymyxin B Sulfate containing oxytetracycline hydrochloride and polymyxin B sulfate; Pfizer Inc., 235 East 42d Street, New York, N.Y. 10017 (NDA 61-015).

Chloromycetin-Polymyxin Ophthalmic Ointment containing chloramphenicol and polymyxin B sulfate; Parke, Davis and Co., Joseph Campan at the River, Detroit, Mich. 48232 (NDA 50-203).

Polysporin Ophthalmic Ointment containing polymyxin B sulfate and zinc bacitracin; Burroughs Wellcome & Co., 3030 Cornwallis Road, Research Triangle Park, N.C. 27709 (NDA 61-220).

The Food and Drug Administration concludes that these drugs for ophthalmic and/or otic use are effective for the indications described in the labeling conditions in this announcement.

Preparations containing these drugs are subject to the antibiotic procedures pursuant to section 507 of the Federal Food, Drug, and Cosmetic Act. After 60 days following publication of this announcement in the *Federal Register*, drugs in the dosage forms described above, for which certification is requested should contain labeling information in accord with this reevaluation of the drugs published in this announcement.

The above-named firms and any other holders of applications approved for a drug of the kinds described above are requested to submit within 60 days following publication of this announcement in the *Federal Register*, amendments to their antibiotic applications to provide for revised labeling. The label for ointments for ophthalmic use should state whether the product is or is not sterile. The labeling should comply with all requirements of the Act and regulations, bear adequate information for safe and effective use of the drug, and be in accord with the guidelines for uniform labeling published in the *Federal Register* of February 6, 1970. The "Indications" section of the labeling should be as follows:

**INDICATIONS**

Oxytetracycline Hydrochloride with Polymyxin B Sulfate Ophthalmic/Otic Ointment.

interests are urged to consolidate or coordinate their presentations.

In the event that the response to this notice of hearing is such that insufficient time is available to accommodate the full amount of time requested in the notices of participation received, the Commissioner shall allocate the available time among the persons making the oral presentation to be used as they wish. Formal written statements on the issues may be presented to the presiding officer on the day of the hearing for inclusion into the administrative record.

The hearing shall be open to the public. Any interested person may be heard with respect to matters relevant to the issues under consideration.

Dated: December 8, 1976.

JOSEPH P. HITE,  
Associate Commissioner for  
Compliance.

[FR Doc. 76-36566 Filed 12-9-76; 11:10 am]

[Docket No. 76N-0472; DEB 6343]

**—HYALURONIDASE—**

Drugs for Human Use; Drug Efficacy Study Implementation; Followup Notice and Opportunity for Hearing

In notices published in the FEDERAL REGISTER of September 23, 1970 (35 FR 14800) (Docket No. FDC-D-235 (now Docket No. 76N-0472)) and June 23, 1972 (37 FR 12418), the Food and Drug Administration announced its conclusions regarding the effectiveness of the drug products described below containing hyaluronidase. The drug products are used as an adjunct to enhance the absorption of drugs in tissue.

Final conclusions concerning hyaluronidase drug products were announced in the June 23, 1972 notice, classifying them as effective or lacking substantial evidence of effectiveness for various indications. The June 23, 1972 notice did not offer an opportunity for hearing concerning the indications that were reclassified in that notice to lacking substantial evidence of effectiveness. This notice offers an opportunity for hearing concerning them and states the conditions for marketing the drug for the indications for which it continues to be regarded as effective. Persons who wish to request a hearing may do so on or before January 10, 1977.

The notice that follows does not pertain to the indications stated in the September 23, 1970 notice to lack substantial evidence of effectiveness. No person requested a hearing concerning them, and they are no longer allowable in labeling. Any such product labeled for those indications is subject to regulatory action.

1. NDA 6-343; Wydase Solution and Wydase Lyophilized; Wyeth Laboratories, Division American Home Products Corp., Box 8299, Philadelphia, PA 19101.

2. NDA 6-714; AHase; Searle Laboratories, Division G. D. Searle & Co., Box 5110, Chicago, IL 60680.

3. NDA 7-933; Hyszyme; Abbott Laboratories, Pharmaceutical Products Division, 14th and Sheridan Rd., D-351, North Chicago, IL 60064.

The following drug product was neither submitted for review by the National Academy of Sciences-National Research Council nor included in the September 23, 1970 and June 23, 1972 notices, but the conclusions described in this notice apply to it.

NDA 6-392; Hydronase; Schering Corp., Gallop Hill Rd., Kenilworth, NJ 07033.

Such drugs are regarded as new drugs (21 U.S.C. 321(p)). Supplemental new drug applications are required to revise the labeling in and to update previously approved applications providing for such drugs. An approved new drug application is a requirement for marketing such drug products.

In addition to the holder(s) of the new drug application(s) specifically named above, this notice applies to all persons who manufacture or distribute a drug product, not the subject if an approved new drug application, that is identical, related, or similar to a drug product named above, as defined in 21 CFR 310.6. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to a drug product named in this notice by writing to the Food and Drug Administration, Bureau of Drugs, Division of Drug Labeling Compliance (HFD-310), 5600 Fishers Lane, Rockville, MD 20852.

**A. Effectiveness classification.** The Food and Drug Administration has reviewed all available evidence and concludes that the drug is effective for the indications listed in the labeling conditions below. The drug lacks substantial evidence of effectiveness for the probably and possibly effective indications which were reclassified in the June 23, 1972 notice.

**B. Conditions for approval and marketing.** The Food and Drug Administration is prepared to approve abbreviated new drug applications and abbreviated supplements to previously approved new drug applications under conditions described herein.

1. **Form of drug.** The drug is in sterile solution or powder for reconstitution and is suitable for injection.

2. **Labeling conditions.** a. The label bears the statement, "Caution: Federal law prohibits dispensing without prescription."

b. The drug is labeled to comply with all requirements of the act and regulations, and the labeling bears adequate information for safe and effective use of the drug. The indications are as follows:

For use as an adjunct to increase the absorption and dispersion of other injected drugs; for hypodermoclysis; as an adjunct in subcutaneous urography for improving the resorption of radiopaque agents.

3. **Marketing status.** a. Marketing of such drug products that are now the subject of an approved or effective new drug application may be continued provided that, on or before February 8, 1977, the holder of the application submits, if he has not previously done so, (1) a supplement for revised labeling as needed to be in accord with the labeling conditions described in this notice, and complete container labeling if current container labeling has not been submitted, and (2) a supplement to provide updating information with respect to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1(c)) to the extent required in abbreviated applications (21 CFR 314.1(f)).

b. Approval of an abbreviated new drug application (21 CFR 314.1(f)) must be obtained prior to marketing such product. Marketing prior to approval of a new drug application will subject such products, and those persons who caused the products to be marketed, to regulatory action.

**C. Notice of opportunity for hearing.** On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 605 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111(a)(5), demonstrating the effectiveness of the drug(s) for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice.

Notice is given to the holder(s) of the new drug application(s), and to all other interested persons, that the Director of the Bureau of Drugs proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug application(s) and all amendments and supplements thereto providing for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice on the ground that new information before him with respect to the drug product(s), evaluated together with the evidence available to him at the time of approval of the application(s), shows there is a lack of substantial evidence that the drug product(s) will have all the effects it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling. An order withdrawing approval will not issue with respect to any application(s) supplemented, in accord with this notice, to delete the claim(s) lacking substantial evidence of effectiveness.

In addition to the ground for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because

it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act pursuant to the exemption for products marketed prior to June 25, 1938, contained in section 201(p) of the act, or pursuant to section 107(c) of the Drug Amendments of 1962; or for any other reason.

In accordance with the provisions of section 505 of the act (21 U.S.C. 355) and the regulations promulgated thereunder (21 CFR Parts 310, 314), the applicant(s) and all other persons who manufacture or distribute a drug product which is identical, related, or similar to a drug product named above (21 CFR 310.6), are hereby given an opportunity for a hearing to show why approval of the new drug application(s) providing for the claim(s) involved should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of a drug product named above and all identical, related, or similar drug products.

If an applicant or any person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for hearing, he shall file (1) on or before January 10, 1977, a written notice of appearance and request for hearing, and (2) on or before February 3, 1977, the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

The failure of an applicant or any other person subject to this notice pursuant to 21 CFR 310.6 to file timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by such person not to avail himself of the opportunity for a hearing concerning the action proposed with respect to such drug product and a waiver of any contentions concerning the legal status of such drug product. Any such drug product labeled for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice may not thereafter lawfully be marketed, and the Food and Drug Administration will initiate appropriate regulatory action to remove such drug products from the market. Any new drug product marketed without an approved NDA is subject to regulatory action at any time.

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of

fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing.

All submissions pursuant to this notice of opportunity for hearing shall be filed in quintuplicate. Such submissions, except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk (address given below) during working hours, Monday through Friday.

Communications forwarded in response to this notice should be identified with the reference number DESI 6343, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852.

Supplements (Identify with NDA number): Division of Surgical-Dental Drug Products (HFD-160), Rm. 1B3-04, Bureau of Drugs.

Original abbreviated new drug applications (Identify as such): Division of Generic Drug Monographs (HFD-530), Bureau of Drugs.

Request for Hearing (Identify with Docket number appearing in the heading of this notice): Hearing Clerk, Food and Drug Administration (HFC-20), Rm. 4-85.

Requests for the report of the National Academy of Sciences-National Research Council: Public Records and Document Center (HFC-18), Rm. 4-82.

Other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD-501), Bureau of Drugs.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050-1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.31) (recodification published in the FEDERAL REGISTER of June 15, 1976 (41 FR 24262)).

Dated: December 1, 1976

J. RICHARD CROUR,  
Director, Bureau of Drugs.

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[Docket No. 76N-0052]

#### OVER-THE-COUNTER DRUGS

##### Decision On Theophylline As A Single Ingredient

The Food and Drug Administration (FDA) announces that, as a result of additional information, the Commissioner of Food and Drugs disagrees with the recommendation of the Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Panel ("the Panel") to allow theophylline to be made available over-the-counter (OTC) as a single ingredient. Any OTC drug product containing theophylline as a single ingredient is subject to immediate regulatory action.

In a notice published in the FEDERAL REGISTER of September 9, 1976 (41 FR 38312), FDA proposed to establish conditions under which OTC cold, cough, allergy, bronchodilator, and antiasth-

matic drugs are generally recognized as safe and effective and not misbranded, based on the recommendations of the Panel. The preamble to the proposal also included the complete conclusions and recommendations of the Panel.

The Panel's recommendations, and the proposed monograph, included its conclusion that several ingredients were safe and effective for OTC use that previously had been limited to prescription use or had been classified for OTC use at a dosage level lower than that recommended by the Panel. After reviewing those specific ingredients, the Commissioner made an initial determination not to disagree with the Panel's recommendations on the OTC use of a number of ingredients, including the use of theophylline as a single ingredient in OTC drug products. The Panel recommended that the adult daily dosage be 100 to 200 milligrams (mg) every 6 hours, not to exceed 800 mg in 24 hours.

The Commissioner stated, however, that although he did not challenge the judgment of the Panel regarding the safety of theophylline, he believed that there was a scientific issue as to whether the recommended dosage levels were therapeutically effective for a significant, identifiable population of asthmatics. Therefore, the Commissioner noted that theophylline was currently undergoing extensive review within the agency and, consequently, the Panel's recommendation might be subject to modification in the tentative final monograph.

Since publication of the Panel's recommendation, the Commissioner has received additional information that requires him to disagree at this time with the Panel's recommendation that theophylline be made available for use as a single ingredient in OTC drug products. This additional information, which was not available during the Panel's deliberations, indicates that the recommended therapeutic dose may be toxic to some individuals. This information suggests that the safe and effective use of this drug requires careful dosage titration based on theophylline serum concentrations.

In a recent report by Miles Weinberger, M.D. and Leslie Hendeles, Ph.D., "Pharmacotherapy of Asthma," *The Journal of the Maine Medical Association*, 67:9, 255-266, September 1976, the authors reported the relationship between theophylline dosage and the likelihood of achieving both therapeutic effect and toxicity. The report states that at the median effective dose (50th percentile) of 26 milligrams per kilogram per day (mg/kg/day) in 4 divided doses for children (or 1000 mg/day in 4 divided doses for adults), about 25 percent of the patient population is likely to be at risk of toxicity. The report shows that at the upper adult dosage recommended by the Panel, i.e., 800 mg/day, about 40 percent of the patient population will achieve a therapeutic effect; however, about 25 percent is likely to be at risk of toxicity. At the lower adult dosage recommended by the Panel, i.e., 400 mg/day, the report shows that none of the patient population is likely to be at risk of