School of Medicine, 660 W. Redwood Street, Baltimore, Maryland 21201. Article: Electron Microscope, Model JEM 100B. Manufacturer: JEOL, Japan. Intended use of article: The article is intended to be used to study histochemical changes in the lens epithelium after experimental production of cataracts. These include lysomes and enzymes identified by chemical reactions. The exact area in the cell where the enzyme occurs is particularly important to identify. The article will also be used for teaching medical students and Ophthalmology residents the techique of electron microscopy with applied histochemistry. Application received by Commissioner of Customs: October 20, 1975.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

RICHARD M. SEPPA,
Director,
Special Import Programs Division.

[FR Doc.75-30329 Filed 11-10-75;8:45 am]

UNIVERSITY OF WASHINGTON, ET AL.

Consolidated Decision on Applications for Duty-Free Entry of Scientific Articles

The following is a consolidated decision on applications for duty-free entry of scientific articles pursuant to Section 6(c) of the Educational, Scientific, and Cultural Materials Importation Act of 1966 (Public Law 89-651, 80 Stat. 897) and the regulations issued thereunder as amended (40 F.R. 12253 et seq. 15 CFR 701, 1975.)

A copy of the record pertaining to each of the applications in this consolidated decision is available for public review during ordinary business hours of the Department of Commerce, at the Special Import Programs Division, Office of Import Programs, Department of Commerce, Washington, D.C. 20230.

Decision: Applications denied. Applicants have failed to establish that instruments or apparatus of equivalent scientific value to the foreign articles, for such purposes as the foreign articles are intended to be used, are not being manufactured in the United States.

Reasons: Section 301.8 of the Regulations provides in pertinent part:

> The applicant shall on or before the 20th day following the date of such notice, inform the Deputy Assistant Secretary whether it intends to resubmit another application for the same article for the same intended purposes to which the denied application relates. The applicant shall then resubmit the new application on or before the 90th day following the date of the notice of denial without prejudice to resubmission, unless an extension of time is granted by the Deputy Assistant Secretary in writing prior to the expiration of the 90 day period. * * * If the applicant fails, within the applicable time periods specified above, to either (a) inform the Deputy Assistant Secretary whether it intends to resubmit another application for the same article to which the denial without prejudice to resubmission relates, or (b) resubmit the new application, the prior denial without prejudice to resubmission shall have the effect of a final decision by the Deputy Assistant Secretary on the application within the context of § 301.11.

The meaning of the subsection is that should an applicant either fail to notify the Deputy Assistant Secretary of its intent to resubmit another application for the same article to which the denial without prejudice relates within the 20 day period, or fails to resubmit a new application within the 90 day period, the prior denial without prejudice to resubmission will have the effect of a final denial of the application.

None of the applicants to which this consolidated decision relates has satisfied the requirements set forth above, therefore, the prior denials without prejudice have the effect of a final decision denying their respective applications.

Section 301.8 further provides:

> "* * * the Deputy Assistant Secretary shall transmit a summary of the prior denial without prejudice to resubmission to the FEDERAL REGISTER for publication, to the Commissioner of Customs, and to the applicant."

Each of the prior denials without prejudice to resubmission to which this consolidated decision relates was based on the failure of the respective applicants to submit the required documentation, including a completely executed application form, in sufficient detail to allow the issue of "scientific equivalency" to be determined by the Deputy Assistant Secretary.

Docket Number: 75-00321-56-17500. Applicant: University of Washington, Department of Oceanography, WB-10, Seattle, Washington 98195. Article: Recording Current Meter, Model 4. Date of denial without prejudice to resubmission: July 10, 1975.

Docket Number: 75-00301-33-77030. Applicant: Bowman Gray School of Medicine, 300 S. Hawthorne Road, Winston-Salem, N.C. 27103. Article: CPS Coherent NMR Spectrometer. Date of denial without prejudice to resubmission: July 18, 1975.

Docket Number: 75-00406-44-01100. Applicant: Tulane University School of Medicine, 1430 Tulane Avenue, New Orleans, Louisiana 70112. Article: Morgan Transfertest Model B with Associated Gas Analyzers. Date of denial without prejudice to resubmission: July 10, 1975.

Docket Number: 75-00426-33-90000. Applicant: The Johns Hopkins Hospital, 601 North Broadway, Baltimore, Maryland 21205. Article: EMI Scanner System with Magnetic Tape System and High Definition Display Units. Date of denial without prejudice to resubmission: July 18, 1975.

Docket Number: 75-00427-33-46040. Applicant: Veterans Administration Hospital, 4150 Clement Street, San Francisco, Calif. 94121. Article: Electron Microscope, Model EM 201S and accessories. Date of denial without prejudice to resubmission: July 18, 1975.

Docket Number: 75-00431-33-46040. Applicant: University of Nebraska—Lincoln, Dept. of Veterinary Science, College of Agriculture, Lincoln, Nebraska 68503. Article: Electron Microscope, Model EM 201C and accessories. Date of denial without prejudice to resubmission: July 18, 1975.

Docket Number: 75-00483-25-20700. Applicant: University of Rochester, Rochester, New York 14627. Article: Ultra-fast Photodiode with infrared (S-1) Photocathode Mounted with 50 OHM Output and high voltage connectors. Date of denial without prejudice to resubmission: July 10, 1975.

Docket Number: 75-00549-01-63550. Applicant: Medical University of South Carolina, 80 Barre Street, Charleston, S.C. 29401. Article: Polarimeter with Micro-observation Tube. Date of denial without prejudice to resubmission: July 10, 1975.

(Catalog of Federal Domestic Assistance Program No. 11.105, Importation of Duty-Free Educational and Scientific Materials.)

RICHARD M. SEPPA,
Director,
Special Import Programs Division.

[FR Doc.75-30330 Filed 11-10-75;8:45 am]

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

Food and Drug Administration

[Docket No. 75N-0184]

CERTAIN DRUG PRODUCTS CONTAINING AN ANTICHOLINERGIC/ANTISPASMODIC IN COMBINATION WITH A SEDATIVE/TRANQUILIZER; ANTISPASMODIC DRUGS ALONE

Drugs for Human Use; Drug Efficacy Study Implementation; Permission for Drugs to Remain on the Market

A notice was published in the FEDERAL REGISTER of December 14, 1972 (37 FR 26623), informing manufacturers of prescription drugs for human use of the future schedule for implementation of the drug efficacy study. That notice listed certain drugs, together with the justification for their medical need, which may remain on the market pending completion of scientific studies to determine effectiveness, and provided for future additions to or deletions from that list. Other drug products are now being added to that list. The products being added have been widely used in medical practice in the treatment of gastrointestinal disorders. Although none of them have been conclusively proven effective, they are of sufficient medical importance to justify additional study. This notice states the conditions for their continued marketing.

In notices published in the FEDERAL REGISTER of October 21, 1970 (35 FR 16422; DESI 4681), June 18, 1971 (36 FR 11754; DESI 3265), June 22, 1971 (36 FR 11875; DESI 10837), July 27, 1972 (37 FR 15028; DESI 597), and September 18, 1973 (38 FR 26138; DESI 9489), 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 concerning the following drug products. Other products included in

those announcements, but not named herein, are not affected by this notice:

DESI 4681

1. Trasentine Phenobarbital Tablets containing adiphenine hydrochloride 50 mg and phenobarbital 20 mg; Ciba Pharmaceutical Co., 556 Morris Ave., Summit, NJ 07901 (NDA 4–681).

2. Prantal with Phenobarbital Tablets containing diphemanil methylsulfate 100 mg and phenobarbital 16 mg; Schering Corp., 1011 Morris Ave., Union, NJ 07083 (NDA 8–829).

DESI 3265

1. Bentyl Capsules containing dicyclomine hydrochloride 10 mg; Merrell-National Laboratories, Division of Richardson-Merrell, Inc., 110 E. Amity Rd., Cincinnati, OH 45215 (NDA 7–409).

2. Bentyl Injection containing dicyclomine hydrochloride 10 mg/cc; Merrell-National Laboratories (NDA 8–370).

3. Bentyl Syrup containing dicyclomine hydrochloride 10 mg; Merrell-Na-National Laboratories (NDA 7–961).

4. Dactil Tablets containing piperidolate hydrochloride 50 mg; Lakeside Laboratories, Division of Colgate-Palmolive Co., 1707 E. North Ave., Milwaukee, WI 53201 (NDA 8–907).

5. Profenil Tablets containing alverine citrate 120 mg; Smith, Miller and Patch, Inc., 401 Joyce Kilmer Ave., New Brunswick, NJ 08902 (NDA 5–695).

6. Octin Tablets containing isomethepteine mucate 2 grains and Octin Solution containing isomethepteine hydrochloride 100 mg/cc; Knoll Pharmaceutical Co., 30 N. Jefferson Rd., Whippany, NJ 07981 (NDA 6–420).

7. Trocinate Tablets containing thiphenamil hydrochloride 100 mg; Wm. P. Poythress & Co., Inc., 16 N. 22d St., Richmond, VA 23261 (NDA 6–098).

DESI 10837

1. Daritran Tablets, containing oxyphencylimine hydrochloride 5 mg and meprobamate 250 mg; Pfizer Laboratories, Division of Pfizer, Inc., 235 E 42d St., New York, NY 10017 (NDA 12–070).

2. Enarax 5 Tablets containing oxyphencyclimine hydrochloride 5 mg and hydroxyzine hydrochloride 25 mg; and Enarax 10 Tablets containing oxyphencyclimine hydrochloride 10 mg and hydroxyzine hydrochloride 25 mg; J. B. Roerig & Co., Division of Pfizer, Inc., (NDA 11–784).

3. Milpath–200 Tablets containing meprobamate 200 mg and tridihexethyl chloride 25 mg; and Milpath–400 Tablets, containing meprobamate 400 mg and tridihexethyl chloride 25 mg; Wallace Laboratories, Division of Carter-Wallace, Inc., Half Acre Rd., Cranbury, NJ 08512 (NDA 11–043).

4. Pathibamate–200 Tablets containing tridihexethyl chloride 25 mg and meprobamate 200 mg; and Pathibamate–400 Tablets, containing tridihexethyl chloride 25 mg and meprobamate 400 mg; Lederle Laboratories Division, American Cyanamid Co., Pearl River, NY 10965 (NDA 10–837).

DESI 597

1. Bentyl Syrup with Phenobarbital containing dicyclomine hydrochloride 10 mg/5 cc and phenobarbital 15 mg/5 cc; Merrell-National Laboratories (NDA 7–961).

2. Bentyl with Phenobarbital Capsules containing dicyclomine hydrochloride 10 mg and phenobarbital 15 mg; Merrell-National Laboratories (NDA 7–409).

3. Dactil with Phenobarbital Tablets containing piperidolate hydrochloride 50 mg and phenobarbital 16 mg; Lakeside Laboratories, Inc. (NDA 8–907).

4. Antrenyl-Phenobarbital Tablets containing oxyphenomium bromide 5 mg and phenobarbital 15 mg; Ciba Pharmaceutical Co., Division of Ciba-Geigy Corp., 556 Morris Ave., Summit, NJ 07901 (NDA 8–492).

5. Robinul-PH Tablets containing glycopyrrolate 1 mg and phenobarbital 16 mg; and Robinul-PH Forte Tablets containing glycopyrrolate 2 mg and phenobarbital 16 mg; A. H. Robins Co., 1407 Cummings Dr., Richmond, VA 23220 (NDA 12–950).

6. Piptal-PHB Tablets containing pipenzolate bromide 5 mg and phenobarbital 16 mg; and Piptal-PHB Elixir containing pipenzolate bromide 5 mg/5 cc and phenobarbital 16 mg/5 cc; Lakeside Laboratories, Inc. (NDA 9–427).

7. Tricoloid and Phenobarbital Tablets containing tricyclamol chloride 50 mg and phenobarbital 16 mg; Burroughs Wellcome & Co., Inc., 3030 Cornwallis Rd., Research Triangle Park, NC 27709 (NDA 8–910).

8. That part of NDA 8–919 pertaining to Co-Elorine 100 Pulvules containing tricyclamol chloride 100 mg and amobarbital 16 mg; Eli Lilly and Co., P.O. Box 618, Indianapolis, IN 46206.

9. Nactisol Tablets containing poldine methylsulfate 4 mg and sodium butabarbital 15 mg; McNeil Laboratories, Inc., Camp Hill Rd., Fort Washington, PA 19034 (NDA 12–741).

10. Centrine Tablets with Phenobarbital containing aminopentamide sulfate 0.5 mg and phenobarbital 15 mg; Bristol Laboratories, Division of Bristol-Myers Co., Thompson Rd., P.O. Box 657, Syracuse, NY 13201 (NDA 9–288).

11. Centrine Elixir with Phenobarbital containing aminopentamide sulfate 0.5 mg/5 cc and phenobarbital 20 mg/5 cc; Bristol Laboratories, (NDA 8–885).

12. Profenil Phenobarbital Tablets containing alverine citrate 120 mg and phenobarbital 15 mg; Smith, Miller and Patch, Inc., (NDA 6–471).

13. Cantil with Phenobarbital Tablets containing mepenzolate bromide 25 mg and phenobarbital 16 mg, Lakeside Laboratories, Inc., (NDA 10–679).

14. Banthine with Phenobarbital Tablets containing methantheline bromide 50 mg and phenobarbital 15 mg; G. D. Searle & Co., P.O. Box 5110, Chicago, IL 60680 (NDA 7–390).

15. That part of NDA 8–942 pertaining to Pamine PB Tablets containing methscopolamine bromide 2.5 mg and phenobarbital 15 mg; The Upjohn Co., 7171 Portage Rd., Kalamazoo, MI 49002.

16. Daricon PB Tablets containing oxyphencyclimine hydrochloride 5 mg and phenobarbital 15 mg; Pfizer Laboratories (NDA 13–515).

17. Tral with Phenobarbital Tablets containing hexocyclium methylsulfate 25 mg and phenobarbital 15 mg; Abbott Laboratories, 14th and Sheridan Rd., N. Chicago, IL 60064 (NDA 10–599).

18. Pro-Banthine with Phenobarbital Tablets containing propantheline bromide 15 mg and phenobarbital 15 mg; G. D. Searle & Co. (NDA 9–014).

19. Probital Tablets, containing propantheline bromide 7.5 mg and phenobarbital 15 mg (G. D. Searle) was also referred to in the notice of July 27, 1972. That product was not included in the approved NDA but is affected by the conclusions in this notice as a related drug.

20. Monomeb Tablets containing penthienate bromide 5 mg and mephobarbital 32 mg; Winthrop Laboratories, 90 Park Ave., New York, NY 10016 (NDA 9–032).

21. Trocinate with Phenobarbital Tablets containing thiphenamil hydrochloride 100 mg and phenobarbital 16 mg; Wm. P. Poythress & Co., Inc., (NDA 6–098).

22. Metropine with Phenobarbital Tablets containing methylatropine nitrate 1 mg and phenobarbital 15 mg; Pennwalt Prescription Products Division, 755 Jefferson Rd., Rochester, NY 14623 (NDA 4–298).

23. Phenobarbital and Atropine Tablets containing atropine sulfate 1/220 grain and phenobarbital ¼ grain; The Vale Chemical Co., Inc., 1201 Liberty St., Allentown, PA 18102 (NDA 0–597).

DESI 9489

Pathilon with Phenobarbital Tablets, containing tridihexethyl chloride 25 mg and phenobarbital 15 mg; Lederle Laboratories (NDA 9–489). This product was not reviewed by the Academy.

The following drug products are subjects of NDA's but were not reviewed by the Academy and have not been the subject of a previous DESI notice. Some are subjects of abbreviated NDA's submitted pursuant to a DESI notice. All are affected by this notice.

1. Librax Capsule, containing clidinium bromide 2.5 mg and chlordiazepoxide 5 mg; Roche Laboratories, Division of Hoffmann-LaRoche, Inc., Nutley, NJ 07110 (NDA 12–750). The new drug application was approved prior to 1962. However, approval of the NDA was withdrawn January 26, 1966 (31 FR 1015), following the occurrence of accentuated anticholinergic effects and the discovery that certain lots of the drug contained greater than usual amounts of impurities which were analogues of clidinium. On September 1, 1966, the new drug application was reinstated after the firm submitted new data including new test procedures to detect the amount of impurities. However, since this reinstatement approval was not based upon a complete review of the entire application and did

not constitute a determination that all claimed indications are supported by substantial evidence of effectiveness, exclusion of Librax from NAS–NRC review was in appropriate. The clinical data included in the new drug application have now been reviewed by the Food and Drug Administration and it has been concluded that the data do not provide substantial evidence of effectiveness of the fixed combination. In addition to deficiencies with respect to the elements of adequate and well-controlled clinical investigations set forth in 21 CFR 314.111 (a)(5), the studies were not designed to show compliance with the requirements of 21 CFR 300.50 *Fixed-Combination prescription drugs for humans*. There is therefore no substantial evidence that the addition of chlordiazepoxide to clidinium bromide contributes to the effectiveness of the latter in the adjunctive therapy of peptic ulcer disease.

2. Spacolin Tablets containing alverine citrate 120 mg; Philips Roxane Laboratories, Inc., 330 Oak St., Columbus, OH 43216 (ANDA 80–634).

3. Dicyclomine Hydrochloride Capsules 10 mg; Bolar Pharmaceutical Co., Inc., 130 Lincoln St., Copiaque, NY 11726 (ANDA 83–179).

4. Dicyclomine Hydrochloride Capsules 10 mg; J. Davis Laboratories Inc., 433 Commercial Ave., Palisades Park, NJ 07650 (ANDA 83–860).

5. Dicyclomine Hydrochloride Tablets 20 mg; J. Davis Laboratories Inc. (ANDA 83–924).

6. Dicyclomine Hydrochloride Capsules 10 mg; The Lannett Co., Inc., 9000 State Rd., Philadelphia, PA 19136 (ANDA 84–285).

7. Dicyclomine Hydrochloride Capsules 10 mg; Danbury Pharmacal Inc., 131 West St., Danbury, CN 06810 (ANDA 84–347).

8. Dicyclomine Hydrochloride Tablets 20 mg; Bolar Pharmaceutical Co., Inc. (ANDA 84–361).

9. Dicyclomine Hydrochloride Tablets 20 mg; Barr Laboratories Inc., Northvale, NJ 07647 (ANDA 84–600).

10. That part of NDA 5–695 pertaining to Profenil Injection, containing alverine hydrochloride 45 mg/cc; Smith, Miller & Patch. Profenil Tablets containing alverine *citrate*, same NDA, was reviewed by the Academy and is listed above under DESI 3265.

All identical, related, and similar drug products, not the subject of an approved new drug application, are covered by the applications reviewed and are subject to this notice. (21 CFR 310.6). Any person who wishes to determine whether a specific product is covered by this notice should write the Food and Drug Administration, Bureau of Drugs, Division of Drug Labeling Compliance (HFD–310), 5600 Fishers Lane, Rockville, MD 20852.

Numerous products containing one or more belladonna alkaloids plus a barbiturate are known to be marketed without an approved new drug application. They are also affected by this notice. Following are some examples of such products, although this is not intended to be an exhaustive list:

1. Barbidonna Tablets and Elixir; Mallinckrodt Chemical Works, Pharmaceutical Division, 2d & Mallinckrodt Sts., St. Louis, MO 63160.

2. Belbarb Tablets; Arnar-Stone Laboratories, Inc., 601 E. Kensington Rd., Mount Prospect, IL 60056.

3. Belladenal Tablets and Elixir; Sandoz Pharmaceuticals, Inc., Rte. 10, E. Hanover, NJ 07936.

4. Butibel Tablets and Elixir; McNeil Laboratories, Inc., Camp Hill Rd., Fort Washington, PA 19034.

5. Chardonna Tablets, William H. Rorer, Inc., 500 Virginia Dr., Fort Washington, PA 19034.

6. Donnatal Tablets, Capsules, and Elixir; A. H. Robins Co., Inc.

7. Donphen Tablets; Lemmon Pharmacal Co., Sellersville, PA 18960.

8. Hybephen Tablets and Elixir; Beecham-Massengill Pharmaceuticals, Division of Beecham, Inc., 501–551 Fifth St., Bristol, TN 37620.

9. Kinesed Tablets; Stuart Pharmaceuticals, Division of I.C.I. America, Inc., 3411 Silverside Rd., Wilmington, DL 19899.

10. Levsin Tablets, Elixir, and Injection; Kremers-Urban Co., 5600 W. County Line Rd., P.O. Box 2038, Milwaukee, WI 53201.

11. Phenobarbital and Belladonna Tablets; The Upjohn Co.

12. Sidonna Tablets; Reed & Carnrick, 30 Boright Ave., Kenilworth, NH 07033.

The DESI notices cited above classified the combination products which they covered as possibly effective for certain indications and lacking substantial evidence of effectiveness for all other indications, and the single-entity drug products as effective with less-than-effective indications.

I. The Combination Drug Products

The anticholinergic/antispasmodic-sedative/tranquilizer combinations reviewed by the NAS–NRC, Drug Efficacy Study Group Panels and by the Food and Drug Administration were in all cases rated as less than effective (none were higher than "possibly effective") as fixed combinations. The anticholinergic components of the combinations were considered effective as "adjunctive therapy in the treatment of peptic ulcer" and the sedative components effective for sedation. Since publication of the initial notices, the FDA has not received information that would alter the conclusion that the combinations have not been demonstrated to be effective. The Commissioner of Food and Drugs has now considered these products further in light of the following.

A. Evidence of Effectiveness

The nature of the evidence needed to demonstrate effectiveness is determined by the condition(s) for which a drug is indicated. Two kinds of indications can be considered for anticholinergic-sedative combinations. First, they could be indicated for treatment of specific gastrointestinal diseases, e.g., for treatment of peptic ulcer disease or functional bowel syndrome. Alternatively, they could be indicated for treatment of two independent diseases; that is, for a gastrointestinal disease when there is also anxiety.

If the combinations are indicated for treatment of the gastrointestinal disease alone, then evidence of their effectiveness must be derived from studies which demonstrate, as required by 21 CFR 300.50 *Fixed-combination prescription drugs for humans*, that the anticholinergic drug and the sedative each contribute to the treatment of the gastrointestinal disease. This is accomplished by showing that the combination improves some gastrointestinal clinical parameter (rate of healing, pain, nausea, rate of recurrence) better than either single ingredient. It should be stressed that evaluation of the effectiveness of the drugs in treating anxiety in these patients is irrelevant to proof of effectiveness for the gastrointestinal indication, since it is the gastrointestinal disease that is being treated. (It might be of interest, however, to evaluate anxiety in order to determine whether there is a particular subclass of patients with gastrointestinal disease who respond best to combinations.)

Although alternative indications could be proposed, it is fairly clear that the anticholinergic-sedative combinations are intended by most physicians to treat gastrointestinal diseases, rather than two independent diseases, because it is thought that anxiety or tension, even if not at a level needing treatment if there were no gastrointestinal disease, contributes to the development of the gastrointestinal diseases or causes exacerbation of their symptoms and that sedation or relief of anxiety may therefore be helpful. This is a reasonable hypothesis and is supported by the known increase in acid secretion in humans with stress, by the well-described ability of stress to produce ulcer disease in animals, and by anecdotal evidence of symtomatic exacerbation of human gastrointestinal disease in periods of stress or anxiety. Although the hypothesis that sedation may be of benefit in treatment of gastrointestinal diseases is a plausible one, there are no adequate and well-controlled studies of any of the anticholinergic / antispasmodic - sedative/tranquilizer combinations which provide substantial evidence, as required by 21 CFR 300.50, that each component in fact contributes to the healing or other improvement of peptic ulcer disease or functional bowel disease. At a meeting of the FDA Gastrointestinal Drugs Advisory Committee on December 16, 1974, Dr. Stanley Lorber, a gastroenterologist who has strongly advocated continued availability of the combinations (see below), agreed with the committee that he knew of no adequate and well-controlled studies which demonstrated the contribution of each component of the combinations.

In addition to such evidence, the FDA combination policy requires that the components be present in a "dosage * * * (amount, frequency, duration) such that the combination is safe and effective for a significant population requiring such

concurrent therapy as defined in the labeling for the drug." This requirement raises the question of whether the effectiveness of the combination would depend on the ability to titrate each component independently. This question, however, obviously cannot be addressed at all until the contribution of each component is demonstrated.

It could be contended that the drugs are indicated, not for treatment of a gastrointestinal disease alone, but for treatment of two independent conditions, a gastrointestinal disease and anxiety, when the two conditions coexist. The implication of such an indication is that the two independent conditions coexist in a significant population, perhaps because they are not truly independent but tend to be associated, and that this population is definable in drug labeling and *requires* both drugs concurrently at the precise dosage (amount, duration of therapy, frequency of therapy) that is available in the fixed combination. The treatment population would thus have to have both the gastrointestinal disease and an anxiety episode needing treatment (i.e., a physician seeing such a patient without any gastrointestinal disease at all but with the same degree of anxiety would prescribe a sedative/tranquilizer in the amount present in the combination). Moreover, there would need to be evidence that the gastrointestinal disease and the anxiety arose and disappeared more or less simultaneously, so that neither drug was given for a condition that was no longer present.

There has been no evidence submitted to the FDA demonstrating that the population needing such concurrent therapy for the two coexisting conditions exists. The requirements of 21 CFR 300.50 are thus not fulfilled for this indication.

B. EVIDENCE OF MEDICAL NEED

In the court order of October 11, 1972, by Judge William B. Bryant of the U.S. District Court for the District of Columbia, which set time requirements for implementation of the Drug Efficacy Study, provision was made in Paragraph XIV for a limited number of drugs to "remain on the market pending completion of scientific studies to determine effectiveness where there is a compelling justification of the medical need for the drug."

Anticholinergic-sedative combinations are widely prescribed for the treatment of gastrointestinal diseases and are perceived as important in such treatment by many specialists in gastroenterology. Dr. Stanley Lorber, Professor of Medicine and Chairman of the Deparement of Gastroenterology of Temple University asked 105 physicians, most of them directors of gastroenterology training programs, to sign a letter to the Director of the Bureau of Drugs, supporting continued availability of the combinations. Of the 58 who responded, 45 supported the letter, which described the combinations as "useful in the treatment of a variety of gastrointestinal diseases and disorders * * *, constructed in such a way as to insure optimum safety with effectiveness . . . , well accepted by gastroenterologists as well as by general practitioners." The letter also stated that "65 percent to 75 percent of prescriptions written for anticholinergics/antispasmodics are prescribed in association with sedative drugs" and that "The potential disadvantages to patients, practicing physicians, and clinical investigators which would result from the removal of these combinations from the formulary and the subsequent need to re-prove their efficacy, when such efficacy has been been recognized for decades, would be a therapeutic injustice as well as an investigative burden of immense proportions. The latter would divert funds and investigative resources away from useful channels." Copies of Dr. Lorber's letter and pertinent portions of the minutes of the meeting of the FDA Gastrointestinal Drugs Advisory Committee have been placed on file in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4-65, 5600 Fishers Lane, Rockville, MD 20852 and may be seen in that office Monday through Friday between 9:00 a.m. and 4:00 p.m. except on Federal legal holidays.

Standard texts also indicate that there are recognized experts in gastroenterology who perceive sedation as an important element in treating gastrointestinal diseases, although this view is far from unanimous and many experts indicate that the usefulness of sedation is not established.

Thus, while "Harrison's Principles of Internal Medicine" (Ref. 1) cautions against the routine use of sedation (p. 1437) and notes that sedatives have not been shown to alter the course of duodenal ulcer materially, "Cecil-Loeb Textbook of Medicine" (Ref. 2) states that while sedatives and tranquilizers do not affect gastric secretion, they promote relaxation and sleep and "rest and relief of tension are important" in treatment of ulcer disease (p. 1274). Small doses of sedative/tranquilizers are mentioned, the same doses generally present in the anticholinergic-sedative combinations. This view is more strongly advocated in "Drugs of Choice 1974-1975" (Ref. 3) (p. 297), which states that "Emotional tension plays an important role in the pathogenesis of peptic ulcer * * *. The relief of anxiety, tension, and other emotional stresses, therefore, is an important therapeutic consideration. Mild sedatives such as phenobarbital, 15 to 30 mg 4 times daily, facilitate rest and relaxation. Chloriazepoxide (Librium), in doses of 5 to 25 mg 3 or 4 times daily, is useful in decreasing anxiety." There is no specific reference to combinations, but the description plainly includes the dosages of sedatives most commonly included in the combinations.

REFERENCES

1. Silen, W., "Peptic Ulcer," *Harrison's Principles of Internal Medicine*, 7th ed. Edited by Wintrobe, M. W. et al., McGraw-Hill, New York, 1974.

2. Kirsner, J. B., "Acid-Peptic Disease," *Cecil-Loeb Textbook of Medicine*, 13th ed. Edited by Beeson, P. B. and W. McDermott, W. B. Saunders Co., Philadelphia, 1971.

3. Rakatansky, H. and J. B. Kirsner, "Drugs for Gastrointestinal Diseases," *Drugs of Choice 1974-1975*. Edited by Modell, W., C. V. Mosby Co., St. Louis, 1974.

Similar assertion of the usefulness of sedation is made in reference to functional bowel disorders ("Drugs of Choice," p. 310), emotional tension being cited as "the most important and most common cause of functional gastrointestinal distress." Combinations of antispasmodics and sedatives are specifically recommended.

It must be emphasized that neither Dr. Lorber's letter nor the opinions offered in standard textbooks constitute in any way evidence that the anticholinergic-sedative combinations are effective. The Commissioner does not accept the view that demonstration of the effectiveness of the anticholinergic-sedative combinations would be a useless diversion of investigative resources, or the conclusion, supported by no reports of adequate and well-controlled studies, that the effectiveness of the combinations has been recognized for decades. The very fact that use of these products is extensive is strong argument for the importance of carrying out studies to determine whether that use is effective.

At the same time, the important role of sedation and anticholinergic-sedative combinations perceived by numerous experts in gastroenterology and the claimed importance of the drugs to patient convenience and selection of proper dosage represent a compelling justification of their medical need and a basis for permitting the combinations to remain available while adequate and well-controlled studies are carried out to determine their effectiveness.

In addition to the medical need for these products represented by their present importance to many gastroenterologists and general practitioners, there are two additional considerations in placing these products under the Paragraph XIV exemption.

First, it is recognized by the Gastrointestinal Drugs Advisory Committee and the Food and Drug Administration that studies of drugs, including combination drugs, for treatment of the common gastrointestinal diseases are difficult to design and conduct because definition of the disease and rating of the severity of illness is difficult, end points of success are difficult to define and measure, and the diseases are placebo-responsive and spontaneously fluctuating in their severity. In part for these reasons, adequate studies of the combinations have not been carried out. The conclusion that there is no substantial evidence of effectiveness of the combinations thus represents predominantly a conclusion that there are no good data, rather than strong evidence that the combinations are not effective. For several years, manufacturers have been attempting to design, and agree with the Food and Drug Administration on, protocols for studies that would be well-controlled; but only recently has FDA, with the help of the new Gastrointestinal Drugs Advisory Committee, been able to provide guide-

lines for such studies. The lack of adequate studies of the anticholinergic-sedative combinations thus is, at least in part, a result of undeveloped investigational methodologies in this area.

Second, the question of the effectiveness of the fixed-dose anticholinergic-sedative combinations cannot be separated from the larger issue of whether sedatives, in variable combination or alone, are effective therapy for gastrointestinal diseases. Although no sedative is at present approved as effective for treating peptic ulcer disease or its symptoms or for treating functional bowel syndrome, sedative-tranquilizers are well-known to be used for these conditions, often with anticholinergics. These uses are not being extensively studied, and there appears to be little incentive to do so when the drugs are generally available and when many potential investigators, such as the signers of the letter to the Director, believe sedatives are already known to be effective. Studies of the fixed-dose combinations will thus provide information that is of great importance to the rational practice of gastroenterology: evidence of whether or not sedation, an important element in current treatment of peptic ulcer disease and functional bowel syndrome, is in fact an effective part of such treatment.

For the above reasons, the Commissioner of Food and Drugs has concluded that combinations of an anticholinergic/antispasmodic drug and a sedative/anti-anxiety drug, should be added to the list of drugs which may remain on the market beyond the applicable time limits for implementation (37 FR 26623). However, continued marketing will depend upon fulfillment of specific requirements, namely, the carrying out, according to protocols that are satisfactory to the Food and Drug Administration, of studies intended to resolve in a timely manner the question of whether or not such drugs are in fact effective (21 CFR 300.50 and 21 CFR 314.111(a)(5)).

Some of the anticholinergic-sedative combinations considered by the NAS/NRC contain only 8 mg of barbiturate. This is well below the therapeutic dose and does not appear to represent a likely unit of titration. These products have not been exempted and are the subject of a separate notice appearing elsewhere in this issue of the FEDERAL REGISTER.

Certain products reviewed by the NAS/NRC contain an anticholinergic in combination with a major tranquilizer. Since these major tranquilizers have not been shown to be effective as sedatives or as antianxiety agents in non-psychotic patients, the combinations containing them lack the rationale of the anticholinergic-sedative combinations and they have not been exempted. They are the subject of a separate notice appearing elsewhere in this issue of the FEDERAL REGISTER.

II. CERTAIN SINGLE-ENTITY ANTICHOLINERGIC DRUGS

In the announcement published in the Federal Register of June 18, 1971 (36 FR 11754; DESI 3265), the Commissioner of Food and Drugs announced his conclusions concerning the single-entity anticholinergic drugs. These were considered to be effective for use as adjunctive therapy in the treatment of peptic ulcer and probably effective in the irritable bowel syndrome. The pediatric preparations were probably effective for use in the treatment of infant colic. A number of drug products which lack anti-secretory properties entirely, are not anticholinergic drugs, and had not claimed effectiveness in ulcer disease except to relieve "spasm" were included erroneously in this list: products containing dicyclomine hydrochloride, piperidolate hydrochloride, alverine citrate, thiphenamil hydrochloride, isometheptene mucate, and isometheptene hydrochloride. In a separate notice appearing elsewhere in this issue of the FEDERAL REGISTER the Director, Bureau of Drugs, announces his conclusion that these drugs, in view of their lack of anti-secretory activity, lack substantial evidence of effectiveness as adjunctive therapy in the treatment of peptic ulcer and are less than effective (probably effective) for the irritable bowel syndrome. These drugs, however, may have advantages in the latter condition, in that they lack the anti-secretory effects of most anticholinergics and may produce fewer side effects as a result. In addition, the difficulties in designing protocols for study of functional bowel syndrome has delayed good study of these products, as well as the combinations. For these reasons, these single-entity antispasmodics have been placed on the exempt list.

III. CONTROLLED RELEASE DOSAGE FORMS

The exemption does not apply to controlled-release forms of such products. A notice concerning controlled-release products appears elsewhere in this issue of the FEDERAL REGISTER.

Accordingly, a new section is added to the list of drugs which may remain on the market (paragraph 3 of the notice of December 14, 1972) to read as follows:

XVIII. ANTICHOLINERGIC/ANTISPASMODIC-SEDATIVE/TRANQUILIZER COMBINATION DRUGS AND ANTISPASMODIC DRUGS ALONE

Class A. Anticholinergic drugs in combination with a sedative/tranquilizer

Any of the following anticholinergic drugs: aminopentamide sulfate, anisotropine methylbromide, atropine sulfate, clidinium bromide, glycopyrrolate, hexocyclium methyl sulfate, hyoscine hydrobromide, hyscyamine sulfate, mepenzolate bromide, methantheline bromide, methscopolamine bromide, methylatropine, nitrare, oxyphencyclimine hydrochloride, oxyphenonium bromide, penthienate bromide, pipenzolate bromide, poldine methylsulfate, propantheline bromide, tricyclamol chloride, or tridihexethyl chloride, in combination with an effective dose of one of the following sedatives or minor tranquilizers:

Sedatives: amobrabital, butabarbital, mephobarbital, phenobarbital, or other intermediate-duration barbiturates;

Minor tranquilizers: chlordiazepoxide, hydroxyzine, meprobamate.

Class B. *Antispasmodic drug alone or in combination with a sedative/tranquilizer.*

Any of the following antispasmodic drugs alone or in combination with an effective dose of a sedative or minor tranquilizer listed under Class A: adiphenine hydrochloride, alverine citrate, alverine hydrochloride, dicyclomine hydrochloride, isometheptene hydrochloride, isometheptene mucate, piperidolate hydrochloride, or thiphenamil hydrochloride.

A number of FEDERAL REGISTER notices were published classifying many of these drugs in combination as less than effective (possibly effective) for their labeled indications. At the present time there is no substantial evidence that any of these products are effective combinations meeting the requirements of 21 CFR 300.50, or that the single-entity antispasmodic drug products are effective for any indication. It is recognized, however, that well-controlled studies of drugs for peptic ulcer disease and functional bowel syndrome are difficult to design and conduct because definition of the diseases and rating of the severity of illness are difficult, end-points of success are difficult to define and measure, and the diseases are placebo-responsive and spontaneously fluctuating in their severity. Only in recent months has the Food and Drug Administration been able to develop guidelines for study of these conditions.

Antispasmodic - sedative / tranquilizer combinations and single-entity antispasmodic drugs are widely used in the treatment of peptic ulcer disease and functional bowel syndrome and are perceived as important and useful tools of therapy by many gastroenterologists and general practitioners, the loss of which would result in poorer and less convenient therapy for their patients. While this perception cannot in any way substitute for well-controlled studies, it does provide a compelling justification for permitting the continued marketing of these drugs while studies are underway to determine whether or not they are in fact effective. Furthermore, in addition to providing information about the fixed-dose combinations under consideration, such studies will provide important data about the use in general (i.e., alone and as variable combinations as well as fixed combinations) of anti-anxiety agents in the treatment of gastrointestinal diseases. Such use is common but is not an approved use for any sedative/tranquilizer because there is a lack of substantial evidence that this use is effective in relieving any gastrointestinal symptom or affecting the course of any gastrointestinal disease. Well-controlled studies of these drugs are thus of great importance to the rational practice of gastroenterology.

Because of the importance in day-to-day practice of these drugs, the need to develop information on this widely used class of drugs, and the difficulty of planning and conducting studies of the common gastrointestinal diseases, these products are being permitted to remain on the market pending completion of scientific studies to determine effectiveness. The specific conditions under which

these drugs may be marketed are as follows:

1. *Labeling.* Class A drugs shall be labeled as possibly effective as adjunctive therapy in the treatment of peptic ulcer and as possibly effective in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis.

Class B drugs, if combinations, shall be labeled as possibly effective in the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis or, if single entities, shall be labeled as probably effective for the same indications. Single-entity pediatric antispasmodic drugs shall be labeled as probably effective for use in the treatment of infant colic.

The exemption does not apply to controlled-release forms of such products.

2. *Studies.* a. On or before February 9, 1976, the manufacturer or distributior of any such product shall submit a protocol to the Division of Cardio-Renal Drug Products, Gastrointestinal Drug Products Group (HFD–110), Bureau of Drugs, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852 for at least two adequate and well-controlled studies by independent investigators or for a multi-clinic study in which the data of at least three investigators can be evaluated independently, to determine whether or not the product is effective for at least one of the indications.

These protocols shall be compatible with Bureau of Drugs guidelines for such studies, available from the Division of Cardio-Renal Drug Products.

The Bureau of Drugs will review submitted protocols within a 90-day period and will provide to the manufacturer or distributor notice of approval or comments.

b. Within 6 months after receipt of the Bureau's approval or comments on the protocol, studies shall be in progress and the manufacturer or distributor shall so notify the Division of Cardio-Renal Drug Products in writing.

c. At 6-month intervals after studies have begun, the manufacturer or distributor shall submit a progress report to include the number of patients and investigators in the studies, the number of studies completed, and the number continuing.

d. Within 18 months after receipt of the Bureau's approval or comments on the protocol, the manufacturer or distributor shall submit data to the Division of Cardio-Renal Drug Products.

3. It will be acceptable to the Food and Drug Administration for manufacturers of products containing the same ingredients at the same dosages or dosage ratios to conduct studies in cooperation with one another and to submit a joint protocol. For this purpse, all barbiturates may be considered as identical.

Failure of any manufacturer or distributor of such drug products, whether or not his drug is the subject of a new drug application, to comply with the requirements of this notice, or to show adequate progress, will result in regulatory action to remove the drug product from the market.

All submissions (e.g., protocol, progress report) pursuant to this notice shall be identified by including the following in a box in the upper portion of the cover letter:

PARAGRAPH XIV DRUG—CATEGORY XVIII (Identify as appropriate, e.g. ANTICHOLINERGIC-SEDATIVE COMBINATION, ANTISPASMODIC)

This notice is issued pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 505, 701, 52 Stat. 1052–1053, as amended, 1055–1056, as amended, (21 U.S.C. 355, 371)), the Administrative Procedure Act (5 U.S.C. 553, 554), and under authority delegated to the Commissioner (21 CFR 2.120).

Dated: November 5, 1975.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.75-30273 Filed 11-10-75;8:45 am]

MICROBIOLOGICAL GUIDELINES AND CRITERIA FOR TESTING CONTACT LENSES MADE WITH NEW POLYMERS

Notice of Availability

The Commissioner of Food and Drugs has developed microbiological guidelines and criteria for testing contact lenses made with new polymers (other than polymethylmethacrylate (PMMA)). These guidelines were developed by the Food and Drug Administration with the assistance of consultants and the Food and Drug Administration's Ophthalmic Drugs Advisory Committee. The guideline's purpose is to (1) provide the microbiological criteria by which contact lenses made with new polymers (other than PMMA) can be approved for marketing, and (2) provide an outline of tests to be performed by manufacturers to ascertain if such criteria have been met. The criteria are intended to minimize the risk of introducing pathogenic organisms into the eye as a consequnece of using contact lenses made with new polymers. These guidelines are not designed to be specific in all details. On request of the sponsor, protocols for studies will be reviewed by the Food and Drug Administration prior to initiation of the studies.

A copy of the draft guidelines has been placed on public display in the office of the Hearing Clerk, Food and Drug Administration, Rm. 4–65, 5600 Fishers Lane, Rockville, MD 20852, and will be available for public inspection Monday through Friday, from 9 a.m. to 4 p.m. Copies of the draft are also available upon request from the Hearing Clerk. Such requests shall be in writing.

Interested persons may, on or before December 11, 1975, submit to the Hearing Clerk written comments, preferably in quintuplicate, on these draft guidelines. Received comments may be seen in the Hearing Clerk's office during working hours, Monday through Friday.

Dated: November 5, 1975.

SAM D. FINE,
Associate Commissioner for Compliance.

[FR Doc.75-30278 Filed 11-10-75;8:45 am]

[Docket No. 75N-0185; DESI 3265]

CERTAIN SINGLE-ENTITY ANTISPASMODIC DRUGS

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

In an announcement (DESI 3265; Docket No. FDC–D–303 (Now Docket No. 75N–0185; NDA 3–265 etc.)) published in the FEDERAL REGISTER of June 18, 1971 (36 FR 11754), the Food and Drug Administration announced its conclusion that the drugs described below are effective as adjuncts in the treatment of peptic ulcer and less than effective for other indications. The Director of the Bureau of Drugs has now concluded that these particular products are not effective adjuncts to peptic ulcer treatment and proposes to withdraw approval of that indication and also certain other indications which were not supported by substantial evidence of effectiveness. Persons wishing to request a hearing must do so on or before December 11, 1975. Other drugs were also included in the announcement of November 18, 1971, but are not affected by this notice.

1. Bentyl Capsules containing dicyclomine hydrochloride 10 mg; Merrell-National Laboratories, Division of Richardson-Merrell, Inc., 110 E. Amity Rd., Cincinnati, OH 45215 (NDA 7–409).

2. Bentyl Injection containing dicyclomine hydrochloride 10 mg/cc; Merrell-National Laboratories (NDA 8–370).

3. Bentyl Syrup containing dicyclomine hydrochloride 5mg/5cc; Merrell-National Laboratories (NDA 7–961).

4. Dactil Tablets containing piperidolate hydrochloride 50 mg; Lakeside Laboratories, Division of Colgate-Palmolive Co., 1707 E. North Ave., Milwaukee, WI 53201 (NDA 8–907).

5. Profenil Tablets containing alverine citrate 120 mg (and Profenil Injection containing alverine hydrochloride 45 mg/cc); Smith, Miller & Patch, Inc., 401 Joyce Kilmer Ave., New Brunswick, NJ 08902 (NDA 5–695). Profenil Injection was not reviewed by the National Academy of Sciences-National Research Council, Drug Efficacy Study Group and was not included in the June 18, 1971 notice, but is regarded as similarly affected.

6. Octin Tablets containing isometheptenemucate 2 grains and Octin Solution containing isometheptene hydrochloride 110 mg/cc; Knoll Pharmaceutical Co., 30 N. Jefferson Rd., Whippany, NJ 07051 (NDA 6–420).

7. Trocinate Tablets containing thiphenamil hydrochloride 100 mg; Wm. P. Poythress & Co., Inc., 16 N. 22d St., Richmond, VA 23217 (NDA 6–098).

The following abbreviated new drug applications, although approved pursuant to the June 18, 1971 notice, are affected by the conclusions below.

1. Spacolin Tablets containing alverine citrate 120 mg; Philips Roxane Laboratories, Inc., 330 Oak St., Columbus, OH 43216 (ANDA 80–634).

2. Dicyclomine Hydrochloride 10 mg Capsules; Bolar Pharmaceutical Co., Inc., 130 Lincoln St., Copiaque, NY 11726 (ANDA 83–179).

3. Dicyclomine Hydrochloride 10 mg Capsules; J. Davis Laboratories, Inc., 433

Commercial Ave., Palisades Park, NJ 07650 (ANDA 83-860).

4. Dicyclomine Hydrochloride 20 mg Tablets; J. Davis Laboratories Inc., (ANDA 83-924).

5. Dicyclomine Hydrochloride 10 mg Capsules; The Lannett Co., Inc., 9000 State Rd., Philadelphia, PA 19136 (ANDA 84-285).

6. Dicyclomine Hydrochloride 10 mg Capsules; Danbury Pharmacal Inc., 131 West St., Danbury, CN 06810 (ANDA 84-347).

7. Dicyclomine Hydrochloride 10 mg Tablets; Bolar Pharmaceutical Co., Inc., (ANDA 84-361).

8. Dicyclomine Hydrochloride 20 mg Tablets; Barr Laboratories Inc., Northvale, NJ 07647 (ANDA 84-600).

All identical, related, or similar products, not the subject of an approved new drug application, are covered by the new drug application(s) reviewed and are subject to this notice (21 CFR 310.6). Any person who wishes to determine whether a specific product is covered by this notice should write to the Food and Drug Administration, Bureau of Drugs, Division of Drug Labeling Compliance (HFD-310), 5600 Fisheries Lane, Rockville, MD 20852.

The announcement of June 18, 1971, stated that the above products, among other single-active-entity products, were regarded as effective for use as adjunctive therapy in the treatment of peptic ulcer, probably effective in the irritable bowel syndrome and adjunctive therapy in neurogenic bowel disturbances (including the splenic flexure syndrome and neurogenic colon), and possibly effective and lacking substantial evidence of effectiveness for other indications. Preparations labeled for pediatric use were regarded probably effective for infant colic.

The evaluations of dicyclomine, piperidolate, alverine, isometheptene, and thiphenamil products in the aforesaid notice as effective adjuncts in the treatment of peptic ulcer was inappropriate. That notice dealt with anticholinergics. These drug entities have not been shown to be effective as anti-secretory agents and in fact possess little or no anticholinergic activity. Further, the sponsors of the products had not previously claimed that they are effective in peptic ulcer disease, except to relieve "spasm". These drug entities are correctly classified as antispasmodics. They continue to be regarded as less than effective (probably effective) for the irritable bowel syndrome and the preparations labeled for pediatric use are regarded as less than effective (probably effective) for infant colic. In that no data were submitted in support of the other less than effective (probably and possibly effective) indications described in the June 18, 1971 notice, those indications are now regarded as lacking substantial evidence of effectiveness.

Accordingly, insofar as the drugs described above are concerned, the revised conclusions are as follows:

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

1. The drugs are less than effective (probably effective) as described in paragraph B below.

2. The drugs lack substantial evidence of effectiveness for adjunctive therapy in the treatment of peptic ulcer and for all the other labeled indications for which they were stated in the notice of June 18, 1971, to be either probably effective or possibly effective.

B. *Labeling conditions.* Labeling revised pursuant to this notice should furnish adequate information for the safe use of the drug for the following less-than-effective (probably effective) indications: the treatment of the irritable bowel syndrome (irritable colon, spastic colon, mucous colitis) and acute enterocolitis and, for pediatric products, infant colic.

C. *Market status.* Because these drug products may have advantages in the irritable bowel syndrome in that they lack the antisecretory effects of most anticholinergics and may produce fewer side effects as a result, and in that difficulties in designing protocols for study of functional bowel syndrome have delayed good study of these products, these single-entity antispasmodics, as well as certain of their combinations, are being placed on the list of drugs which may remain on the market pending completion of scientific studies to determine effectiveness. The specific conditions under which these drugs may be marketed are described in a separate notice published elsewhere in this issue of the FEDERAL REGISTER.

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 505 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 drugs for indications referred to in paragraph A.2 of this notice.

Therefore, notice is given to the holders of the new drug applications, 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 applications and all amendments and supplements thereto on the ground that new information before him with respect to the drug products, evaluated together with the evidence available to him at the time of approval of the applications, shows there is a lack of substantial evidence, for the indications referred to in paragraph A.2 of this notice, that the drug products will have the effect they purport or are 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 supplemented, in accord with the notice, to (1) delete the claim(s) lacking substantial evidence of effectiveness; and (2) revise the labeling to be in accord with the labeling conditions set forth in paragraph B of this notice.

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 and all other persons who manufacture or distribute a drug which is identical, related, or similar to a drug product named above (21 CFR 310.6), are hereby given an opportunity 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 the applicant, or any person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for a hearing he shall file (1) on or before December 11, 1975, a written notice of appearance and request for hearing, and (2) on or before January 12, 1976, 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 the 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 an indication(s) lacking substantial evidence of effectiveness referred to in paragraph A.2 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 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 and 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) Monday through Friday from 9 a.m. to 4 p.m., except on Federal legal holidays.

Communications forwarded in response to this notice should be identified with the reference number DESI 3265, directed to the attention of the appropriate office listed below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20852:

Supplements (identify with NDA number): Division of Cardio-Renal Drug Products (HFD-110), Rm. 16B-30, Bureau of Drugs.

Request for Hearing (identify with docket number): Hearing Clerk, Food and Drug Administration (HFC-20), Rm. 4-65, Parklawn Building.

All other communications regarding this notice: Drug Efficacy Study Implementation Project Manager (HFD-101), Bureau of Drugs.

This notice is issued pursuant to the provisions of 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 2.121).

Dated: October 29, 1975.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc.75-30274 Filed 11-10-75;8:45 am]

[Docket No. 75N-0223; DESI Nos. 597, 3265, 4681]

CERTAIN ANTICHOLINERGIC DRUGS IN CONTROLLED-RELEASE DOSAGE FORM

Notice of Opportunity for Hearing on Proposal To Withdraw Approval of New Drug Applications

In notices published in the FEDERAL REGISTER of October 21, 1970 (35 FR 16422; DESI 4681), June 18, 1971 (36 FR 11754; DESI 3265), and July 27, 1972 (37 FR 15028; DESI 597), the Food and Drug Administration announced its conclusions that certain anticholinergic drugs in controlled-release dosage form, described below, were probably effective, possibly effective, or lacking substantial evidence of effectiveness for use in the treatment of various gastrointestinal disorders (for example, ulcers) for which they were labeled. Since no data demonstrating the claimed prolonged effect have been received, substantial evidence of effectiveness is lacking and withdrawal of approval of these products is now being proposed. Persons wishing to request a hearing on the proposal must do so on or before December 11, 1975. Other products included in the above-listed announcements, but not named herein, are not affected by this notice.

DESI 597

1. Bentyl Repeat Action Tablets with Phenobarbital containing dicyclomine hydrochloride and phenobarbital; Merrell-National Laboratories, Division of Richardson-Merrell, Inc., 110 E. Amity Rd., Cincinnati, OH 45215 (NDA 9-311).

2. Tral with Phenobarbital Gradumets, (controlled-release tablets) containing hexocyclium methylsulfate and phenobarbital; Abbott Laboratories, Abbott Park, 14th & Sheridan Rd., N. Chicago, IL 60064 (NDA 11-200).

3. Pathilon with Phenobarbital Sequels (controlled-release capsules) containing tridihexethyl chloride and phenobarbital; Lederle Laboratories, Division American Cyanamid Co., P.O. Box 500, Pearl River, NY 10965 (NDA 11-940).

DESI 3265

1. Tral Gradumets (controlled-release tablets) containing hexocyclium methylsulfate; Abbott Laboratories (NDA 11-200).

2. Pathilon Sustained Release Capsules containing tridihexethyl chloride; Lederle Laboratories (NDA 11-889).

DESI 4681

1. Prantal Repetabs (controlled-release tablets) containing diphemanil methylsulfate; Schering Corp., Galloping Hill Rd., Kenilworth, NJ 07033 (NDA 8-638).

2. Scopolamine Methyl Bromide Prolongsules (controlled-release capsules) containing methscopolamine bromide; Richlyn Laboratories Inc., 3725 Castor Ave., Philadelphia, PA 19124 (NDA 10-404).

Scopolamine Methyl Bromide Prolongsules (NDA 10-404) was a subject of an order published in the FEDERAL REGISTER of October 27, 1971 (36 FR 20619), withdrawing approval of the new drug application on the ground of failure to submit required reports under section 505(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(j)). At that time no final conclusions concerning effectiveness of this drug had been reached. Conclusions have now been reached and the drug is included here to inform all interested persons of such conclusions and offer them the opportunity to request a hearing.

All of the above drug products have been reclassified as lacking substantial evidence of effectiveness. This reclassification is based upon the lack of any data demonstrating a prolonged duration of effect as compared with the products in standard dosage form.

With respect to the single-entity anticholinergic products (i.e., hexocyclium methylsulfate, tridihexethyl chloride, diphemanil methylsulfate, socpolamine methylbromide): since the standard dosage forms of single-entity anticholinergic products were classified as effective, bioavailability data demonstrating the prolonged effect claimed would permit reclassifying the products to effective.

With respect to the combination products: since, in a notice appearing elsewhere in this issue of the FEDERAL REGISTER, the standard dosage forms of the combination products are being included on the list of drugs which may remain on the market pending completion of scientific studies to determine effectiveness, bioavailability data demonstrating the prolonged effect claimed would permit these products to be added to that list. The required scientific studies could be conducted with either the standard or controlled-release forms of the combinations: the conclusions reached will be considered applicable to both forms.

Data from bioavailability studies may be submitted as part of a request for hearing, subject to the conditions described in 21 CFR 314.200(c)(4). If such data demonstrate the prolonged effect claimed, appropriate action, as discussed above, will be initiated.

On the basis of all of 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 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) and 21 CFR 314.111(a)(5), and, for those products which are combinations, 21 CFR 300.50, demonstrating the effectiveness of any of the drug products listed above.

Therefore, 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) (except for NDA 10-404) (or if indicated above, those parts of the application(s) providing for the drug product(s) listed above and all amendments and supplements thereto 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 the effect it purports or is represented to have under the the conditions of use prescribed, recommended, or suggested in the labeling.