of Agriculture, has prepared a draft environmental impact statement for the Norwalk River Watershed Project, Fairfield County, Connecticut, USDA–SCS–EIS–WS–(ADM)–76–2–D–CT.

The environmental impact statement concerns a plan for watershed protection, flood prevention, and wildlife. The planned works of improvement include conservation land treatment, supplemented by channel work and four water control structures with two pool areas improved for wildlife (one area is within the pool of a structure already constructed). The channel work will involve the enlargement of 11,125 feet of existing channel.

A limited supply of copies is available at the following location to fill single copy requests: Soil Conservation Service, USDA, Mansfield Professional Park, Storrs, Connecticut 06268.

Norwalk River Watershed Project, Connecticut, Notice of Availability of Draft Environmental Impact Statement

Copies of the draft environmental impact statement have been sent for comment to various federal, state, and local agencies as outlined in the Council on Environmental Quality Guidelines. Comments are also invited from others having knowledge or of special expertise on environmental impacts.

Comments concerning the proposed action or requests for additional information should be addressed to Robert G. Halstead, State Conservationist, Soil Conservation Service, Mansfield Professional Park, Storrs, Connecticut 06268.

Comments must be received on or before December 26, 1975, in order to be considered in the preparation of the final environmental impact statement.

(Catalog of Federal Domestic Assistance Program No. 10.904, National Archives Reference Services.)

Dated: October 31, 1975.

JOSEPH W. HAAS,
*Deputy Administrator for Water Resources, Soil Conservation Service.*

[FR Doc.75-30235 Filed 11-10-75;8:45 am]

## DEPARTMENT OF COMMERCE

### Domestic and International Business Administration

### NATIONAL CANCER INSTITUTE

### Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article 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 FR 12253 et seq., 15 CFR 701, 1975).

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

Docket Number: 76–00015–33–46040. Applicant: National Cancer Institute, Baltimore Cancer Research Ctr., 3100 Wyman Park Drive, Baltimore, Maryland 21211. Article: Electron Microscope, JEM 100C. Manufacturer: JOEL Ltd., Japan. Intended use of article: The article is intended to be used in a research capacity in studies of subcellular aspects of differentiation, neoplastic transformation of hematopoietic cells and the response of malignant and normal cells to chemotherapeutic agents. Etiologic factors of human hematopoietic dyscrasias and animal model systems of such diseases are also under investigation. Of particular importance is the search for and identification of virus like structures in human material. The article will also be used to study structural alterations in cellular components such as nucleic acid malformations, subcellular particle alterations and changes in tissue organization by pharmacologic agents or appearing in the natural course of a disease.

Comments: No comments have been received with respect to this application. Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, was being manufactured in the United States at the time the foreign article was ordered (April 8, 1975). Reasons: The foreign article has a specified resolving capability of 3 Angstroms (Å). The most closely comparable domestic instrument is the Model EMU–4C supplied by the Adam David Company. The Model EMU–4C has a specified resolving capability of 5Å. Resolving capability bears an inverse relationship to its numerical rating in Å, i.e., the lower the rating, the better the resolving capability. We are advised by the Department of Health, Education, and Welfare (HEW) in its memorandum dated October 17, 1975 that the best resolution available is pertinent to the purposes for which the foreign article is intended to be used. HEW further advises that domestic instruments did not provide resolution equivalent to that of the foreign article at the time the foreign article was ordered. We, therefore, find that the EMU–4C was not of equivalent scientific value to the foreign article for such purposes as this article is intended to be used at the time the foreign article was ordered.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, which was being manufactured in the United States at the time the article was ordered.

(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.75-30327 Filed 11-10-75;8:45 am]

### PURDUE UNIVERSITY

### Decision on Application for Duty-Free Entry of Scientific Article

The following is a decision on an application for duty-free entry of a scientific article 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 FR 12253 et seq, 15 CFR 701, 1975).

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

Docket Number: 76–00017–33–90000. Applicant: Purdue University, ADMS Building, West Lafayette, IN 47907. Article: Rotating X-ray generator, Model GX20 3.5", Manufacturer: AEI Scientific Apparatus, United Kingdom. Intended use of Article: The article is intended to be used as a high intensity fine focus X-ray source for the investigation of the crystal and molecular structure of small spherical RNA viruses.

Comments: No comments have been received with respect to this application. Decision: Application approved. No instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, is being manufactured in the United States. Reasons: The foreign article provides a focused spot of minimal size (0.1 x 0.1 mm) and rotating target for maximum x-ray beam intensity. The Department of Health, Education, and Welfare (HEW) advised in its memorandum dated October 17, 1975 that the capabilities described above are pertinent to the purposes for which the article is intended to be used. HEW also advised that it knows of no domestic instrument of equivalent scientific value to the foreign article for such purposes as the article is intended to be used.

The Department of Commerce knows of no other instrument or apparatus of equivalent scientific value to the foreign article, for such purposes as this article is intended to be used, which is being manufactured in the United States.

(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.75-30328 Filed 11-10-75;8:45 am]

### UNIVERSITY OF WASHINGTON, ET AL.

### Applications for Duty-Free Entry of Scientific Articles

The following are notices of the receipt of 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). Interested persons may present their views with respect to the question of whether an instrument or apparatus of

equivalent scientific value for the purposes for which the article is intended to be used is being manufactured in the United States. Such comments must be filed in triplicate with the Director, Special Import Programs Division, Office of Import Programs, Washington, D.C. 20230, on or before December 1, 1975.

Amended regulations issued under cited Act (40 FR 12253 et seq. 15 CFR 701, 1975) prescribe the requirements applicable to comments.

A copy of each application is on file, and may be examined during ordinary Commerce Department business hours at the Special Import Programs Division, Department of Commerce, Washington, D.C. 20230.

Docket Number: 76-00159-56-17500. Applicant: University of Washington, Department of Oceanography WB-10, Seattle, Washington 98195. Article: Recording Current Meter, Model 4. Manufacturer: Iva Aanderaa, Norway. Intended use of article: The article is intended to be used for studies of time dependent velocity, temperature, conductivity fields in the Pacific Northwest coastal and estuarine waters. Application received by Commissioner of Customs: October 9, 1975.

Docket Number: 76-00168-85-40600. Applicant: University of Georgia, Department of Geology, Athens, Georgia 30601. Article: Isotope Radio Mass Spectrometer, Model 602C and accessories. Manufacturer: V. G. Micromass, United Kingdom. Intended use of article: The article is intended to be used for the following projects:

(1) Examination of the influence of surface meteoric waters upon subsurface volcanic processes. This feature will be studied through analyses of the $^{18}O/^{16}O$ in rocks and minerals from samples obtained from various localities in Antarctica.

(2) Measurement of $^{18}O/^{16}O$ variations of rocks and minerals for the purpose of ascertaining temperatures attained within major thrust sheets of the northern and central Rocky Mountains.

(3) Examination of $^{18}O/^{16}O$ variations of foraminifera from deep sea cores obtained from the Caribbean Sea. These analyses will be utilized for the purposes of obtaining stratigraphic correlation with already analyzed cores at different localities, and

(4) Examinations of $^{18}O/^{16}O$ $^{13}C/^{12}C$ variations from rocks and minerals related to the iron ore deposits of S. E. Missouri. This study will be conducted for the purpose of obtaining information about the source of waters and the temperatures involved in deposit of these ore bodies.

The article will also be used as an educational tool for students in geology and in other scientific fields such as archeology, chemistry and biology. Application received by Commissioner of Customs: October 16, 1975.

Docket Number: 76-00169-33-46500. Applicant: The University of Texas Health Science Center at San Antonio, Dept. of Anatomy, 7703 Floyd Curl Drive, San Antonio, Texas 78284. Article: Ultramicrotome, Model Om U3 with AO Stereoscopic Microscope. Manufacturer: C. Reichert Optische Werke AG, Austria. Intended use of article: The article is intended to be used for studies of biological specimens of placental tissue from several primate species including human. Studies will be performed to characterize the normal morphology of various primate species comparing one with the other and particularly with the human, and to attempt to correlate differences in structure with abnormal conditions. The article will also be used in the course, "Techniques for Electron Microscopy" to give students an understanding of the principles of histologic technique for electron microscopy and practical experience in actually accomplishing the procedures necessary to produce material for study with the electron microscope. Application received by Commissioner of Customs: October 16, 1975.

Docket Number: 76-00170-33-46500. Applicant: Mount Desert Island Biological Laboratory, Salsbury Cove, Maine 04672. Article: Ultramicrotome, Model LKB 8800A. Manufacturer: LKB Produkter AB, Sweden. Intended use of article: The article is intended to be used for studies of tissue from local marine, fresh water and terrestrial organisms (bony and cartilagenous fish, birds invertebrates, shell fish and hemichordates) and hamsters. Experiments will be conducted to determine ultrastructural and cytochemical properties of epithelial and endothelial tissues that transport ions.. water and macromolecules. Application received by Commissioner of Customs: October 16, 1975.

Docket Number: 76-00171-33-46500. Applicant: University of Massachusetts, Mass. Agricultural Experiment Station, 217 Stockbridge Hall, Amherst, Mass. 01002. Article: Ultramicrotome, Model LKB 8800A. Manufacturer: LKB Produkter AB, Sweden. Intended use of article: The article is intended to be used for studies of biological materials, including plant and animal tissue, viruses and bacteria which exhibit both normal and pathologic structure. A variety of experiments will be conducted involving the structure and behavior of cells and tissues under normal and pathological conditions. The article will also be used for educational purposes in the courses:

(1) Plant Pathology-Plant Virology—concerned with the structure and properties of plant viruses; virus infection and synthesis; virus transmission; symptomatology and physiology of virus-infected plants; assay and purification of plant viruses; as well as identification and control of plant viruses, and

(2) Entomology—Insect Microbiology and Pathology—involving the diseases of insects including classification and biology of the pathogens involved. Application received by Commissioner of Customs: October 16, 1975.

Docket Number: 76-00172-33-19095. Applicant: The Wistar Institute, 36th Street at Spruce, Philadelphia, Pennsylvania 19104. Article: M-86 Combined Scanning Interferometer and Densitometer with accessories. Manufacturer: Vickers, Ltd., United Kingdom. Intended use of article: The article is intended to be used for investigating the involvement of cycling-noncycling cell transitions in a variety of disease processes, especially aging. Cytochemical and autoradiographic preparations of cultured cells as well as biopsy and autopsy material from humans are used in these studies. The article is also intended to be used for the training of predoctoral, postdoctoral, and resident medical students involved in a number of research projects to provide a basic understanding of the cytophotometer and its application to biomedical research. Application received by Commissioner of Customs: October 16, 1975.

Docket Number: 76-00173-00-75000. Applicant: Massachusetts Institute of Technology, Cambridge, Ma. 02139. Article: Cutter Drive Unit for Camkometer. Manufacturer: Cambridge Insitu, United Kingdom. Intended use of article: The article is an accessory to a Camkometer which will be used to measure in situ stresses in a soil mass by providing a means of inserting load cells into the soil with a minimum of disturbance. Application received by Commissioner of Customs: October 16, 1975.

Docket Number: 76-00174-33-90000. Applicant: Loma Linda University, P.O. Box 728, Loma Linda, CA 92354. Article: EMI Scanner System with Magnetic Tape System and Diagnostic Display Console, Data Transfer Module. Manufacturer: EMI Limited, United Kingdom. Intended use of article: The article is intended to be used for research in the following areas:

(1) Cerebro-vascular occlusive disease and cerebral blood flow.

(2) Acute head injuries.

(3) Early detection and treatment of head injuries.

(4) Application of the scanner to ENT Radiology, specifically the orbit and the ear.

The article will also be used in training programs for medical students, medical school faculty, radiology residents, neuroradiology fellows, and radiologic technologists. Application received by Commissioner of Customs: October 20, 1975.

Docket Number: 76-00175-75-40450. Applicant: University of Rochester, AEP, 400 Elmwood Avenue, Rochester, N.Y. 14642. Article: Doserate Meter-Integrator. Manufacturer: Electron Diamonds Ltd., United Kingdom. Intended use of article: The article is intended to be used for the determination of precise location of a struck irradiation source which is essential to avoid inadvertent damage to source encapsulation with consequent environmental contamination when attempting to achieve safe storage of the source. Application received by Commissioner of Customs: October 20, 1975.

Docket Number: 76-00176-35-46040. Applicant: University of Maryland—

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