reconstitution, for intravenous administration.

c. The remainder of the drugs are in tablet form suitable for oral administration.

2. *Labeling conditions.* a. The label bears the statement,

Caution: Federal law prohibits dispensing without prescription.

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

Amodiaquine hydrochloride: For the suppressive treatment and for the treatment of acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*.

Hydroxychloroquine sulfate: For the suppressive treatment and treatment of acute attacks of malaria due to *P. vivax*, *P. malariae*, *P. ovale*, and susceptible strains of *P. falciparum*. It is also indicated for the treatment of discoid and systemic lupus erythematosus, and rheumatoid arthritis.

Glycobiarsol: For the treatment of intestinal amebiasis in adults and children weighing over 80 pounds, but it is not considered to be the drug of choice.

Diethylcarbamazine citrate: For the treatment of Bancroft's filariasis, onchocerciasis, ascariasis, tropical eosinophilia, and loiasis.

Hydroxystilbamidine isethionate: For the treatment of visceral leishmaniasis (kala azar) and American mucocutaneous leishmaniasis. It is also indicated for the treatment of North American blastomycosis, but it is not considered to be the drug of choice.

3. *Marketing status.* a. Marketing of such drug products that are now the subject of an approved or effective new drug application may be continued provided that, on or before October 25, 1977, the holder of the application submits, if he has not previously done so, (i) a supplement for revised labeling as needed to be in accord with the labeling conditions described in this notice, and complete container labeling if current container labeling has not been submitted, and (ii) a supplement to provide updating information with respect to items 6 (components), 7 (composition), and 8 (methods, facilities, and controls) of new drug application form FD-356H (21 CFR 314.1 (c)) to the extent required in abbreviated applications (21 CFR 314.1(f)).

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

C. *Notice of opportunity for hearing.* On the basis of all the data and information available to him, the Director of the Bureau of Drugs is unaware of any adequate and well-controlled clinical investigation, conducted by experts qualified by scientific training and experience, meeting the requirements of section 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 drug(s) for the indication(s) lacking substantial evidence of effectiveness referred to in paragraph A. of this notice.

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

In addition to the ground for the proposed withdrawal of approval stated above, this notice of opportunity for hearing encompasses all issues relating to the legal status of the drug products subject to it (including identical, related, or similar drug products as defined in 21 CFR 310.6), e.g., any contention that any such product is not a new drug because it is generally recognized as safe and effective within the meaning of section 201(p) of the act or because it is exempt from part or all of the new drug provisions of the act pursuant to the exemption for products marketed prior to June 25, 1938, contained in section 201(p) of the act, or pursuant to section 107(c) of the Drug Amendments of 1962; or for any other reason.

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

If an applicant or any person subject to this notice pursuant to 21 CFR 310.6 elects to avail himself of the opportunity for a hearing, he shall file (1) on or before September 26, 1977, a written notice of appearance and request for hearing, and (2) on or before October 25, 1977, the data, information, and analyses on which he relies to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this proposal to withdraw approval. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, a submission of data, information, and analyses to justify a hearing, other comments, and a grant or denial of hearing, are contained in 21 CFR 314.200.

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

A request for a hearing may not rest upon mere allegations or denials, but must set forth specific facts showing that there is a genuine and substantial issue of fact that requires a hearing. If it conclusively appears from the face of the data, information, and factual analyses in the request for the hearing that there is no genuine and substantial issue of fact which precludes the withdrawal of approval of the application, or when a request for hearing is not made in the required format or with the required analyses, the Commissioner will enter summary judgment against the person(s) who requests the hearing making findings and conclusions, denying a hearing.

All submissions pursuant to this notice of opportunity for hearing shall be filed in quintuplicate. Such submissions, except for data and information prohibited from public disclosure pursuant to 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Hearing Clerk between the hours of 9 a.m. and 4 p.m. Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (secs. 502, 505, 52 Stat. 1050–1053, as amended (21 U.S.C. 352, 355)) and under the authority delegated to the Director of the Bureau of Drugs (21 CFR 5.82).

Dated: August 18, 1977.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc.77-24515 Filed 8-25-77;8:45 am]

[Docket No. 77N-0226; DESI 7358]

COMBINATION PRODUCT CONTAINING FURAZOLIDONE WITH KAOLIN AND PECTIN

Withdrawal of Approval of Part of New Drug Application

AGENCY: Food and Drug Administration.

ACTION: Notice.

SUMMARY: This notice withdraws approval of that part of NDA 11-323 pertaining to Furoxone Liquid containing furazolidone with kaolin and pectin. The product has been used as an antibacterial agent.

DATE: Effective September 6, 1977.

ADDRESSES: Requests for opinion of the applicability of this notice to a specific product should be directed to: Division of Drug Labeling Compliance (HFD-310), Bureau of Drugs, Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857.

FOR FURTHER INFORMATION CONTACT:

Ronald L. Wilson, Bureau of Drugs (HFD-32), Food and Drug Administration, Department of Health, Education, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301-443-3650.

SUPPLEMENTARY INFORMATION: In a notice of opportunity for hearing (DESI 7358; Docket No. FDC-D-520 (now Docket No. 77N-0226) published in the FEDERAL REGISTER of March 29, 1973 (38 FR 8186), the Commissioner of Food and Drugs proposed to issue an order withdrawing approval of the new drug application (NDA) for Furoxone Liquid containing furazolidone with kaolin and pectin. The basis of the proposed order was that the drug lacks substantial evidence of effectiveness and is not shown to be safe for use. The holder of the NDA, Norwich Pharmacal Co., filed a request for hearing for the combination product. A notice published in the FEDERAL REGISTER of May 30, 1975 (40 FR 23501) amended March 29, 1973 notice to cite the policy for fixed combination prescription drugs for humans (21 CFR 300.50) because that policy had not been specifically referred to in the March 29, 1973 notice. No data were submitted in response to either notice in support of a hearing for the combination product Furoxone Liquid. By letter of April 28, 1977, Norwich Pharmacal Co. withdrew its hearing request, and approval of the part of the following new drug application pertaining to the product is now being withdrawn:

That part of NDA 11-323 pertaining to Furoxone Liquid containing furazolidone with kaolin and pectin; Norwich Pharmacal Co., division of Morton Norwich, Inc., 17 Eaton Ave., Norwich, NY 13815.

Other products that were included in the March 29, 1973 notice are not affected by this notice, nor is the single-entity Furoxone Liquid containing furazolidone, which was the subject of a FEDERAL REGISTER notice of August 16, 1976 (41 FR 34662).

Any drug product that is identical, related, or similar to the drug product named above, and not the subject of an approved new drug application, is covered by that part of the new drug application reviewed and is 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 Division of Drug Labeling Compliance (HFD-210), (address given above).

No other person filed a written appearance of election with respect to a combination of furazolidone, kaolin, and pectin, as provided by said notice. The failure to file such an appearance constitutes election by such persons not to avail themselves of the opportunity for a hearing.

The Director of the Bureau of Drugs, under the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat 1052-1053, as amended (21 U.S.C. 355)), and under authority delegated to him (21 CFR 5.82), finds that (1) new information before him with respect to the drug product, evaluated together with the evidence available to him at the time of approval of the application, shows there is a lack of substantial evidence that the drug product will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in its labeling; and (2) tests by methods not deemed reasonably applicable when the application was approved, evaluated together with the evidence available when the application was approved, reveal that the drug is not shown to be safe for use under the conditions of use on the basis of which the application was approved.

Therefore, pursuant to the foregoing finding, approval of that part of new drug application 11-323 pertaining to the combination product Furoxone Liquid, and all amendments and supplements applying thereto, is withdrawn effective September 6, 1977.

Shipment in interstate comerce of the above product or of any identical, related, or similar product, not the subject of an approved new drug application, will then be unlawful.

Dated: August 18, 1977.

J. RICHARD CROUT,
Director, Bureau of Drugs.

[FR Doc.77-24514 Filed 8-25-77;8:45 am]

[Docket No. 77N-0030]

GRAS AND PRIOR-SANCTIONED HUMAN FOOD INGREDIENTS

Availability of Information; Correction

AGENCY: Food and Drug Administration.

ACTION: Correction.

SUMMARY: In FR Doc. 77-16637, appearing on page 30431 in the FEDERAL REGISTER of Tuesday, June 14, 1977, the following correction is made in the table on page 30432: In the table labeled "Reports of the select committee," the ordering number for the substance "Agar-agar" should read, "PB-265-502/AS."

FOR FURTHER INFORMATION CONTACT:

Corbin I. Miles, Bureau of Foods (HFF-335), Food and Drug Administration, Department of Health, Education, and Welfare, 200 C St. SW., Washington, D.C. 20204, 202-472-4750.

Dated: August 22, 1977.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.77-24749 Filed 8-25-77;8:45 am]

[Docket No. 77N-0240]

SINGLE-ENTITY CORONARY VASODILATORS

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

AGENCY: Food and Drug Administration (FDA).

ACTION: Notice.

SUMMARY: This notice announces (1) the availability of guidelines and methods for evaluating the bioavailability and effectiveness of coronary vasodilators, and (2) the specific conditions under which these products may be marketed while such studies are in progress.

DATES: Notices of intent to conduct bioavailability studies are due on or before September 26, 1977.

Bioavailability studies must be initiated on or before November 25, 1977.

Clinical studies of effectiveness must be completed and submitted by FDA by August 27, 1979.

ADDRESSES: Communications in response to this notice should be identified with the NDA or ANDA number (if any) and the following in a box in the upper portion of the cover letter: "Paragraph XIV Drug—Category I; Coronary Vasodilator" directed to the attention of the office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, Md. 20857.

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

Abbreviated New Drug Applications: Division of Generic Drug Monographs (HFD-530), Bureau of Drugs.

Requests for guidelines for bioavailability studies: Division of Biopharmaceutics (HFD-520), Rm. 16-62, Bureau of Drugs.

Requests for guidelines for clinical studies: Division of Cardio-Renal Drug Products (HFD-110), Rm. 16B-30, Bureau of Drugs.

Requests for opinion of the applicability of this notice to a specific product: Division of Drug Labeling Compliance (HFD-310), Bureau of Drugs.

All other submissions required by this notice: Division of Cardio-Renal Drug Products (HFD-110), Rm. 16B-30, Bureau of Drugs.

FOR FURTHER INFORMATION CONTACT:

Robert H. Hahn, Bureau of Drugs (HFD-32), Food and Drug Administration, Department of Health, Educa-

tion, and Welfare, 5600 Fishers Lane, Rockville, Md. 20857, 301–443–3650.

SUPPLEMENTARY INFORMATION: In notices published in the FEDERAL REGISTER on February 17, 1971 (36 FR 3078) (DESI 12836) and February 25, 1972 (37 FR 4001 (DESI 1786), FDA published its conclusions pursuant to evaluation of reports from the National Academy of Sciences-National Research Council (NAS/NRC), Drug Efficacy Study Group concerning conventional and controlled release dosage forms of certain coronary vasodilators, stating that the drugs are possibly and probably effective and lacking substantial evidence of effectiveness for their labeled indications.

A notice was published in the FEDERAL REGISTER of December 14, 1972, informing manufacturers and distributors of prescription drugs for human use of the order entered October 11, 1972, by Judge William B. Bryant of the U.S. District Court for the District of Columbia, directing the future schedule for implementation of the Drug Efficacy Study. Paragraph XIV of the court order provided that a limited number of drugs, for which there is compelling justification of medical need, may remain on the market pending completion of scientific studies to determine their effectiveness, and it provided for future additions to or deletions from that list. These drugs are referred to as "paragraph XIV drugs." The drugs listed in Category I in that notice are conventional dosage forms of certain coronary vasodilators containing a single active drug entity. A notice was published in the FEDERAL REGISTER of July 11, 1973 (38 FR 18477), and corrected on July 25, 1973 (38 FR 19920), adding other such drugs to the list. Pursuant to petitions to permit controlled release forms of the drugs also to remain on the market pending clinical studies to determine effectiveness, the July 11, 1973 notice provided that controlled release forms could remain on the market on a product-by-product basis pending completion of scientific studies showing that the product is released in a defined manner, which would permit qualified products to be added to the list of drugs allowed to remain on the market pending completion of clinical trials to determine effectiveness. The notice required that data from such studies be submitted to the Food and Drug Administration no later than November 1, 1973. For reasons set forth below, this proved impossible. By this notice, the Commissioner is formally adding controlled release dosage forms of certain of these drugs to Category I under paragraph XIV. These are now being included on the same basic justification as the conventional forms, together with several additional factors relevant to their medical need. Given the prophylactic purpose of these drugs in treatment of angina, a prolonged duration of action can provide a significant advantage. While there is an effective drug for prophylaxis of angina that can be taken as little as three times per day (propranolol), some patients cannot tolerate this alternative longer acting drug and must turn to a drug of the organic nitrate class. Although certain conventional release products in this class are labeled for four times daily dosage, it is not at all certain and appears unlikely, that they will prove to have a 6 hour duration of action. It is therefore important to determine whether the controlled release formulations can provide a reasonably prolonged action and it is appropriate for these products to remain available for patients while this is determined. As evidenced by current usage patterns, many angina patients prefer a dosage form that may have a longer effect and thus be taken less frequently than conventional forms. Methods not available when the July 11, 1973 notice was published are now available and are suitable for evaluating controlled release as well as conventional forms. If controlled release forms are ultimately shown to be effective, their prolonged activity would be of significant benefit to angina patients.

Also now being included are certain dosage forms of nitroglycerin and of erythrityl tetranitrate. Although they were not included in the Drug Efficacy Study, they are regarded as related drugs which should be studied for bioavailability and effectiveness.

Therefore, Category I published in the December 14, 1972 notice, as amended by the July 11, 1973 notice, is amended to read as follows:

I. CORONARY VASODILATORS (ANTIANGINAL DRUGS) (SINGLE ACTIVE DRUG ENTITY)

Isosorbide dinitrate (sublingual, chewable, and conventional oral forms and controlled release forms).

Mannitol hexanitrate (conventional oral and controlled release forms).

Trolnitrate phosphate (conventional oral and controlled release forms).

Pentaerythritol tetranitrate (conventional oral and controlled release forms).

Nitroglycerin (topical ointment forms, conventional oral forms, and controlled release forms).

Dipyridamole (conventional oral form).

Erythrityl tetranitrate (sublingual, conventional oral, and chewable forms, and controlled release forms).

It has been difficult to determine the bioavailability and effectiveness of the organic nitrate class of antianginal drugs. Effectiveness has been difficult to measure because of the relative insensitivity and variability of the clinical measures used in the evaluation of these drugs. Bioavailability has also been difficult to determine because these drugs are extensively metabolized and conventional blood or urine assay methods are not applicable. Suitably sensitive chemical assay methods for routine use with this class of drugs do not exist at present. Even if it were possible to meaure these drugs and their metabolites in biological fluids, the clinical and pharmacological significance of the blood level of any given metabolite would still be unclear. Although several sponsors submitted physiologic studies to support bioavailability, only one of these studies was found adequate to even suggest that an orally administered organic nitrate may be sufficiently bioavailable to possibly have some clinical effectiveness. The development of appropriate physiologic methods, however, had not been adequately addressed by investigators. For these reasons the requirements set forth in the December 14, 1972 and July 11, 1973 notices have not been met by manufacturers of coronary vasodilator drug products. The possible medical importance of these drugs, including controlled release dosage forms, remains, however, and FDA has sought to overcome some of the methodological deficiencies impeding evaluation of this drug class.

Under FDA sponsorship, research was conducted in an effort to develop methods for evaluating the bioavailability of the antianginal drug products that do not depend on blood level measurements of nitrates. Guidelines and methods for the evaluation of the physiological effects and comparative bioavailability of organic nitrate antianginal drug products were developed by Victor F. Smolen, Ph. D. and Edward J. Williams, Ph. D., School of Pharmacy and Pharmacal Sciences, Purdue University, West Lafayette, Indiana 47907. (The project was entitled "A Study of Drug Bioavailability as Related to Physiological Respone," Food and Drug Administration Contract No. 223–73–3023). This work clearly indicates that physiologic response monitoring can provide reliable, sensitive, convenient, and meaningful measures of the drugs' bioavailability, although at this time this method cannot be used to assess clinical effectiveness. Demonstration of such effectiveness requires the performance of clinical trials. If physiologic responses can be shown to correlate well with clinical effectiveness, then it may be possible in the future to rely upon physiologic response studies to assess the effectiveness of newly formulated organic nitrate drug products.

The FDA-sponsored studies indicate that response variables derived from digital plethysmography (DPG) and electrocardiographic recordings are useful measures of the bioavailability of organic nitrate drugs, i.e., can demonstrate that sufficient drug has been absorbed to elicit a positive measurable indication of pharmacologic activity. Although many response variables appear to show some association with bioavailability, including: (1) Diastolic amplitude, (2) systolic amplitude, (3) cardiac output computed as the products of systolic pulse pressure and heart rate, (4) heart rate, (5) DPG, (6) apparent left ventricular ejection time, and (7) systolic time interval, heart rate and diastolic amplitude appear to correlate best. While Dr. Smolen, the original investigator, acquired his data in a form which could be and was computerized, all of these measurements, except for cardiac output, can readily be manually obtained directly from DPG strip chart recordings without the need for expensive and sophisticated recording and

computational equipment. Copies of the detailed guidelines and methods developed by Dr. Smolen for the evaluation of the physiologic responses and comparative bioavailability of organic nitrate antianginal drug products are available on request from the Division of Biopharmaceutics.

As a result of the availability of new and adequate methods for determining the bioavailability of not only the conventional and controlled release forms of coronary vasodilators, but of the sublingual, chewable, and topical forms as well, the Commissioner is now able to state definitively the conditions for their marketing. Those conditions are set forth in this notice and include requirements for both bioavailability and clinical testing. The demonstration of bioavailability had not previously been a prerequisite to conducting clinical trials of the conventional dosage forms. The time required to conduct and analyze clinical trials, however, is often great, and there is no valid reason to permit continued marketing of a drug product during this period if there is little likelihood that the drug will prove effective. It is thus appropriate to require demonstration of bioavailability as an indication of the possibility of effectiveness before permitting a drug to be marketed during clinical testing. Bioavailability testing may also aid in choosing proper dosages and dose intervals for the clinical trials.

As stated in the DESI notices cited above, such products are regarded as new drugs (21 U.S.C. 321(p)). Continued marketing, will, therefore, only be permitted for coronary vasodilator products whose sponsors first perform adequate studies that demonstrate the bioavailability of their products, and subsequently conduct well-controlled studies to demonstrate clinical effectiveness; in addition, an abbreviated new drug application (ANDA) will be required for any product now on the market without an approved new drug application. The Food and Drug Administration intends to act at the earliest possible date to remove from the market products not fulfilling the conditions of this notice.

Following is a list of new drug applications providing for single entity coronary vasodilators. Not all of these were specifically reviewed by the NAS/NRC or named in a DESI notice. Those which were reviewed by the Academy and named in DESI notices are identified by DESI numbers.

DESI 1786

a. Metamine Tablets containing trolnitrate phosphate; Pfizer Laboratories, Division Charles Pfizer & Co., Inc., 235 East 42nd St., New York, NY 10017 (NDA 8-294).

b. Metamine Sustained Tablets containing trolnitrate phosphate; Pfizer, Inc. (NDA 10-131).

c. Nitretamine and Nitretamine-10 Tablets containing trolnitrate phosphate; Squibb Pharmaceutical Co., Division of E. R. Squibb & Sons, Inc., P.O. Box 4000, Princeton, NJ 08540 (NDA 9-196).

d. Penta-Erythritol Tetranitrate Nyscaps containing pentaerythritol tetranitrate; USV Laboratories, Division USV Pharmaceutical Corp., 1 Scarsdale Rd., Tuckahoe, NY 10707 (NDA 12-317).

e. Peritrate Tablets containing pentaerythritol tetranitrate; Warner-Chilcott Laboratories, Division of Warner-Lambert Pharmaceutical Co., 201 Tabor Rd., Morris Plains, NJ 07950 (NDA 8-072).

f. Peritrate SA Tablets containing pentaerythritol tetranitrate; Warner-Chilcott Laboratories (NDA 11-109).

g. Pencard and Pencard No. 2 Tablets containing pentaerythritol tetranitrate; Cole Pharmacal Co., P.O. Box 14404, St. Louis, MO 63108 (NDA 8-852).

h. Maxitate Tablets containing mannitol hexanitrate; Pennwalt Prescription Products Division, P.O. Box 1766, Rochester, NY 14603 (NDA 1-786).

i. Nitranitol Tablets containing mannitol hexanitrate; Merrell-National Laboratories, Division of Richardson-Merrell, Inc., P.O. Box 15260, Cincinnatti, OH 45215 (NDA 3-193).

j. Mannitol Hexanitrate Tablets; S. F. Durst and Co., Inc., Division of O'Neal, Jones, and Feldman, Inc., 1683 Winchester Rd., Philadelphia, PA 19020 (NDA 4-730).

k. Isordil Tablets containing isosorbide dinitrate; Ives Laboratories, Inc., 685 Third Ave., New York, NY 10017 (NDA 12-093).

l. Isodril Sublingual Tablets containing isosorbide dinitrate; Ives Laboratories, Inc. (NDA 12-940).

m. Timed Pentryate Stronger Capsules containing pentaerythritol tetranitrate; Fellows-Testagar, Subdivision of Chromalloy Pharmaceuticals, Inc., 12741 Capital Ave., Oak Park, MI 48237 (NDA 12-646).

n. Pentestan-80 Stancaps containing pentaerythritol tetranitrate; Standex Laboratories, 585 West Second Ave., Columbus, OH 43215 (NDA 12-488).

o. Pentritol Tempules containing pentaerythritol tetranitrate; Armour Pharmaceutical Co., Greyhound Tower, Phoenix, AZ 85077 (NDA 12-311).

p. Duotrate-45 Plateau Caps containing pentaerythritol tetranitrate; Marion Laboratories, Inc., 10236 Bunker Ridge Rd., Kansas City, MO 64137 (NDA 12-748).

q. Metranil Duracaps containing pentaerythritol tetranitrate; Meyer Laboratories, Inc., 1900 W. Commercial Blvd., Ft. Lauderdale, FL 33309 (NDA 12-529).

r. Tetraaule-80 Timesules containing pentaerythritol tetranitrate; Storck Pharmaceuticals, Inc., Division Arnar-Stone Laboratories, Inc., 601 East Kensington Rd., Mount Prospect, IL 60056 (NDA 12-450).

s. Nitroglyn Sustained Action Tablets containing nitroglycerin; Key Pharmaceuticals, Inc., P.O. Box 3670, Miami, FL 33169 (NDA 9-599).

t. Isordil Tembids containing isosorbide dinitrate; Ives Laboratories, Inc. (NDA 12-882).

DESI 12836

Persantine Tablets containing dipyridamole; Geigy Pharmaceuticals, Division of Ciba-Geigy Corp., Ardsley, NY 10502 (NDA 12-836).

THE FOLLOWING NDA'S WERE NOT REVIEWED BY THE NAS/NRC

1. Metamine Tablets containing trolnitrate phosphate; Leeming / Paquin, Division Charles Pfizer & Co., Inc., 235 East 42nd St., New York, NY 10017 (NDA 8-798).

2. Sorbitrate (Sublingual and Oral) Tablets containing isosorbide dinitrate; Stuart Pharmaceuticals, Division of I.C.I. United States, Inc., P.O. Box 751, Wilmington, DE 19899 (NDA's 16-191 and 16-192 respectively).

3. Pentaerythritol Tetranitrate Tablets; Philips Roxane Laboratories, Division of Philips Roxane, Inc., P.O. Box 1739, Columbus OH 43216 (NDA 16-425).

4. Vasitol Tablets containing pentaerythritol tetranitrate; Rowell Laboratories, Inc., 210 Main St., West Baudette, MN 56623 (NDA 16-436).

5. Tranite Tablets containing pentaerythritol tetranitrate; Westfield Laboratories, Inc., Division of O'Neal, Jones, & Feldman, Inc., 3941 Brotherton Rd., Cincinnati, OH 45209 (NDA 16-445).

6. Dipentrate Tablets containing pentaerythritol tetranitrate; Invenex Pharmaceuticals, Division of The Mogul Corp., 2303 Schultz Rd., St. Louis, MO 63141 (NDA 16-449).

7. Pentaerythritol Tetranitrate Tablets; Kirkman Laboratories, Inc., P.O. Box 3929, Portland, OR 97208 (NDA 16-459).

8. Nitrin Tablets containing pentaerythritol tetranitrate; The Vale Chemical Co., Inc., 1201 Liberty St., Allentown, PA 18102 (NDA 16-502).

9. Pentaerythritol Tetranitrate Tablets; Davis-Edwards Pharmacal Corp., Backus Ave., Danbury, CN 06810 (NDA 16-537).

10. Pentaerythritol Tetranitrate Tablets; Lit Drug Co., 2530 Polk St., Union, NJ 07083 (NDA 16-545).

11. Pentran Tablets containing pentaerythritol tetranitrate; Halsey Drug Co., Inc., 1827 Pacific St., Brooklyn, NY 11233 (NDA 16-553).

12. Pentaerythritol Tetranitrate Tablets; Zenith Laboratories, Inc., 140 LeGrand Ave., Northvale, NJ 07647 (NDA 16-555).

13. Pentaerythritol Tetranitrate Tablets; West-Ward, Inc., 745 Eagle Ave., Bronx, NY 10456 (NDA 16-558).

14. Pentaerythritol Tetranitrate Tablets; Stanlabs, Inc., Box 3108, Portland, OR 97208 (NDA 16-561).

15. Pentaerythritol Tetranitrate Tablets; Tutag Pharmaceuticals, Inc., 2599 W. Midway Blvd., Broomfield, CO 80020 (NDA 16-567).

16. Pentaerythritol Tetranitrate Tablets; American Pharmaceutical Co., Inc., P.O. Box 448, Passaic, NJ 07055 (NDA 16-593).

17. Pentaerythritol Tetranitrate Tablets; Bolar Pharmaceutical Co., Inc., 130 Lincoln St., Copiague, Long Island, NY 11726 (NDA 16-625).

18. Dilivas Tablets containing pentaerythritol tetranitrate; Ferndale Laboratories, Inc., 780 West Eight Mile Rd., Ferndale, MI 48220 (NDA 16-661).

19. Sorbitrate Chewable Tablets containing isosorbide dinitrate; Stuart Pharmaceuticals, Division of I.C.I. United States, Inc. (NDA 16-776).

20. Hydronal Oral Solution containing isosorbide; Stuart Pharmaceuticals, Division of I.C.I. United States, Inc. (NDA 17-063).

21. Corodyl Forte Sustained Release Tablets containing pentaerythritol tetranitrate; Bock Pharmacal Co., 5435 Highland Park Dr., St. Louis, MO 63110 (NDA 12-519).

22. Pent-T-80 Sustained Release Capsules containing pentaerythritol tetranitrate; Merlcon Industries, Inc., 420 S.W. Washington St., Peoria, IL 61602 (NDA 12-613).

23. Tetrate-80 Time Disintegrating Capsules containing pentaerythritol tetranitrate; Pasadena Research Laboratories, Inc., 2107 E. Villa St., Pasadena, CA 91107 (NDA 13-303).

24. Tranite D-Lay Sustained Release Capsules containing pentaerythritol tetranitrate; Westerfield Laboratories, Inc., (NDA 16-499 [1]).

25. Pentitrol Tempules (Sustained Release Capsules) containing pentaerythritol tetra-

[1] Approved post-1962 continent upon future conclusions resulting from the Drug Efficacy Study.

nitrate; Armour Pharmaceutical Co., (NDA 16-457 [1]).

26. Duotrate-30 Plateau Capsules containing pentaerythritol tetranitrate; Marion Laboratories, Inc., (NDA 16-470 [1]).

27. Nitroglyn Sustained Action Tablets; Key Pharmaceuticals, Inc., (NDA 9-599).

28. Nitro-Bid (controlled release) Capsules; Marion Laboratories, Inc., (NDA's 16-518 and 16-975).

29. Nitrong (controlled release) Tablets; Wharton Laboratories, Inc., Division U.S. Ethicals, Inc., 37-02 48th Ave., Long Island City, NY 11101 (NDA 17-384).

30. Nitrospan (controlled release) Capsules; USV Laboratories, Division USV Pharmaceutical Corp., (NDA 16-447).

31. Perispan Timed Disintegration Capsules containing pentaerythritol tetranitrate; USV Laboratories (NDA 12-317).

32. Duotrate-45 Plateau Capsules (sustained release) containing pentaerythritol tetranitrate; Marion Laboratories, Inc. (NDA 12-748).

This notice applies not only to present holders of new drug applications covering the drugs listed but to all persons who manufacture or distribute any drug product that is identical, related, or similar to these, as set forth in 21 CFR 310.6, including erythrityl tetranitrate and nitroglycerin ointment, not the subject of an approved new drug application, except that it does not apply to nitroglycerin in sublingual form. Reference sources such as "American Drug Index" and "Drug Topics Red Book" indicate that numerous firms supply such products. It is the responsibility of every drug manufacturer or distributor to review this notice to determine whether it covers any drug product he manufactures or distributes. Any person may request an opinion of the applicability of this notice to a specific drug product he manufactures or distributes that may be identical, related, or similar to a drug product named in this notice by writing to the Division of Drug Labeling Compliance (address given above).

The Commissioner concludes that any such product, whether or not it is now marketed and whether or not it is now the subject of an approved new drug application, may be marketed in order to fulfil the critical medical need for antianginal preparations with more prolonged activity than sublingual nitroglycerin only if it meets the requirements of this notice. The Commissioner emphasizes that FDA will take regulatory action to terminate marketing of any product not in compliance with this notice.

Requirements for Products NOW Subjects of Approved NDA's

Proceedings to withdraw approval of new drug applications which are in approved status on August 26, 1977, will not be taken provided that each of the following conditions is met:

1. On or before September 26, 1977, an applicant who intends to conduct bioavailability studies for one or more dosage forms notifies the Division of Cardio-Renal Drug Products.

Bioavailability studies are begun by November 25, 1977, and the Division of Cardio-Renal Drug Products is notified within 10 days after studies are begun.

3. Bioavailability studies are completed and submitted to the Division of Cardio-Renal Drug Products within 30 days after their completion or 6 months after their initiation, whichever is earlier.

4. Clinical trials are begun not later than 4 months after notification by FDA that the bioavailability data are satisfactory. They may, of course, be begun earlier than this. (If FDA determines that the bioavailability data do not indicate the product is bioavailable, proceedings will be initiated to withdraw approval of the application and future clinical trials would necessitate an IND.)

5. An analyzed progress report of the clinical trials is submitted annually to the Division of Cardio-Renal Drug Products and a brief progress report is submitted at 6-month intervals.

6. Clinical trials are completed and the results submitted to the Division of Cardio-Renal Drug Products by August 27, 1979. If the studies are completed before that time, the results shall be submitted within 30 days after their completion.

Requirements for Products NOT NOW Subjects of Approved NDA's

Regulatory proceedings to remove from the market such products that were marketed commercially on August 26, 1977, will not be taken provided that each of the following conditions is met:

1. On or before September 26, 1977, the sponsor notifies the Division of Cardio-Renal Drug Products of his intent to conduct bioavailability studies for one or more dosage forms.

2. By November 25, 1977, the sponsor submits an abbreviated new drug application (ANDA) (21 CFR 314.1(f)) for the product(s) to the Division of Generic Drug Monograph (HFD-530), Bureau of Drugs. If the information in the ANDA is complete and satisfactory, it will be conditionally approved, pending results of bioavailability and clinical studies. Such conditionally approved products will have the same legal status as products that are subjects of "deemed approved" applications reviewed in the Drug Efficacy Study; that is, as products for which safety is not in question but for which effectiveness has not been proven.

3. Bioavailability studies are begun by November 25, 1977, and the Division of Cardio-Renal Drug Products is notified within 10 days after studies are begun.

4. Bioavailability studies are completed and submitted to the Division of Cardio-Renal Drug Products within 30 days of their completion or 6 months after their initiation whichever is earlier.

5. FDA has not issued a non-approvable letter to the applicant concerning the ANDA.

6. The ANDA is conditionally approved by May 23, 1978.

7. Clinical trials are begun no later than 4 months after notification by the Division of Cardio-Renal Drug Products that the bioavailability data are satisfactory. They may, of course, be begun earlier than this. (If FDA determines that the bioavailability data do not indicate the product is bioavailable, proceedings will be commenced to withdraw or refuse approval of the application and future clinical trials would necessitate an IND).

8. An analyzed progress report of the clinical trials is submitted annually to the Division of Cardio-Renal Drug Products and a brief progress report is submitted at 6-month intervals.

9. Clinical trials are completed and the results submitted to the Division of Cardio-Renal Drug Products by August 27, 1979. If the studies are completed before that time, the results shall be submitted within 30 days after their completion.

Requirements for Products Entering the Market After August 26, 1977

Regulatory action will not be taken against a product that enters the market after August 26, 1977 provided that each of the following conditions is met:

1. Prior to marketing the product, the sponsor submits an ANDA (21 CFR 314.1(f)) and his commitment to conduct bioavailability and clinical studies. If the information in the ANDA is complete and satisfactory, it will be conditionally approved pending results of bioavailability and clinical studies. Such conditionally approved products will have the same legal status as products that are subject of "deemed approved" applications reviewed in the Drug Efficacy Study; that is, as products for which safety is not in question but for which effectiveness has not been proven.

2. The FDA does not issue a non-approvable letter regarding such application.

3. The ANDA is conditionally approved within 180 days after it is submitted.

4. Bioavailability studies are begun within 10 days after submitting the application.

5. Bioavailability studies are completed and submitted to the Division of Cardio-Renal Drug Products within 30 days after their completion or 6 months after their initiation, whichever is earlier.

6. Clinical studies are begun no later than 4 months after notification by the Division of Cardio-Renal Drug Products that bioavailability data are satisfactory. They may, of course, be begun earlier than this. (If FDA determines that the bioavailability data do not indicate the product is bioavailable, proceedings will be initiated to withdraw or refuse approval of the application and future clinical trials would necessitate an IND.)

7. An analyzed progress report of the clinical trials is submitted annually to the Division of Cardio-Renal Drug Products and a brief progress report is submitted at 6-month intervals.

8. Clinical trials are completed and the results submitted to the Division of Cardio-Renal Drug Products by August 27, 1979. If the studies are completed before that time, the results shall be submitted within 30 days after their completion.

The Commissioner points out that the time limit for completion and submission of clinical studies is the same as for

products already on the market on August 26, 1977. To extend the time simply because a product entered the market after that date is regarded as inconsistent with the FDA policy to resolve effectiveness questions on paragraph XIV drugs at the earliest possible time and to require all marketed products to be subject to testing requirements. Thus, persons desiring to market new products in this category significantly late in the timetable set forth in this notice will probably have to join a collaborative study (discussed below) in order to meet this condition.

BIOAVAILABILITY STUDIES

All products in this category must be tested using either the guidelines that were developed under the FDA (Smolen) contract or another well-documented method. Other methods can be used only if the sponsor submits evidence, in advance, that they are equally applicable and maintains compliance with the schedule described below.

Bioavailability studies must be performed for each dosage form marketed (including controlled release products), but not each strength, provided the formulations involve the same inactive ingredients in approximately the same ratios. It will not be necessary to perform clinical trials with each dosage form provided those dosage forms not subjected to clinical trials are similar in their bioavailability characteristics to the drug products which are tested clinically. If a product with a controlled release claim is tested in clinical trials, it must be compared with a conventional dosage form in such a manner to enable FDA to determine that the prolonged effect of the controlled release product is not due merely to its greater drug content (i.e., dose dumping) and that it is comparable in effect to the immediate release product given at appropriate intervals. If any product is administered at levels which exceed the largest dose recommended for that drug by any of its manufacturers in currently approved or permitted labeling, a Notice of Claimed Investigational Exemption for a New Drug (IND) will be needed for the study.

Guidelines for bioavailability studies are available from the Division of Biopharmaceutics. Sponsors who elect to use alternative methods must obtain advance approval from the Division of Biopharmaceutics, but the times for starting and completing such studies will not be extended beyond those stated above. Upon notification that the submitted bioavailability data are satisfactory, the sponsor must then go on to clinical trials for effectiveness as outlined below. If the bioavailability data are not satisfactory, regulatory action will be taken to remove the drug from the market.

Bioavailability data will be considered satisfactory to permit entry into clinical trials only if the dosage for which a pharmacologic effect is demonstrated does not exceed the largest dose recommended for that drug by any of its manufacturers in currently approved or permitted labeling.

If a firm elects to study clinically a dosage higher than in its current labeling, but no higher than in another firm's labeling, it must do a pilot safety study. While larger doses than this may be studied under an IND, failure to demonstrate that the currently recommended dosage is acceptably bioavailable will be considered grounds for revoking its paragraph XIV exemption, and regulatory action will be taken to remove the drug from the market.

To be considered bioavailable, the product must be tested using an approved protocol and shown to be different, according to criteria set forth in FDA's guidelines for bioavailability, from placebo with respect to its effect on the physiologic measurement during an interval appropriate to the recommended dosing intervals.

CLINICAL STUDIES

After bioavailability data are submitted and FDA determines that they are adequate, clinical trials for effectiveness must be conducted for each coronary vasodilator drug product, except that (1) manufacturers of drugs with the same active ingredient and acceptable bioavailability characteristics may elect to conduct collaborative studies, and (2) manufacturers of several dosage forms of the same drug may choose one of those dosage forms for clinical trials provided that those dosage forms not subjected to clinical trials have bioavailability characteristics similar to those of the selected products. The choice of dosage and dosage interval to be studied may be influenced by the results of bioavailability studies; as noted above, however, the dosage used in studies conducted under the provisions of this notice may not exceed the largest dose recommended for that drug by any of its manufacturers in current permitted or approved labeling.

If a firm elects to study clinically a dosage higher than in its current labeling, but no higher than in another firm's labeling, it must do a small pilot safety study.

Guidelines for the clinical study of coronary vasodilators are available on request from the Division of Cardio-Renal Drug Products as follows:

a. *Sublingual Isosorbide Dinitrate, Sublingual Erythrityl Tetranitrate.* Final guidelines have been developed for the study of a drug in acute angina pectoris by the FDA Cardiovascular-Renal Advisory Committee. These guidelines involve treatment of an acute attack only. Because claims are also being made for prophylaxis of an acute attack, sponsors will also need to develop and submit protocols for study of sublingual isosorbide dinitrate or sublingual erythrityl tetranitrate given prior to an exercise tolerance test.

b. *Oral Organic Nitrates, Controlled Release and Topical Nitroglycerin and Conventional Oral Dipyridamole.* Guidelines that have similarly been developed by the FDA Cardiovascular-Renal Advisory Committee for assessment of oral antianginal investigational new drugs may be utilized for the Phase III clinical studies required to demonstrate effectiveness for the oral organic nitrates, controlled release and topical nitroglycerin and dipyridamole. Bioavailability studies should also be conducted in some patients undergoing clinical trials to attempt to show a correlation between physiologic and clinical effects. It is recommended that such physiologic effects be measured once in the placebo baseline period, at the onset of the drug (or placebo) treatment period, and midway through the treatment period.

All submissions (e.g., notice of intent, protocol, progress report, study results) pursuant to this notice shall be identified by including the NDA or ANDA number and the following in a box in the upper portion of the cover letter:

"Paragraph XIV Drug– Category I: Coronary Vasodilator."

This notice is issued under 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 (U.S.C. 553, 554), and under authority delegated to the Commissioner (21 CFR 5.1).

Dated: August 22, 1977.

WILLIAM F. RANDOLPH,
Acting Associate Commissioner for Compliance.

[FR Doc.77-24750 Filed 8-25-77;8:45 am]

National Institute of Education

PANEL FOR THE REVIEW OF LABORATORY AND CENTER OPERATIONS

Meeting

AGENCY: National Institute of Education.

ACTION: Notice of public meeting.

SUMMARY: This notice sets forth the schedule and proposed agenda of the first meeting of the Panel for the Review of Laboratory and Center Operations. It also describes the function of the Panel. Notice of these meetings is required under the Federal Advisory Committee Act (5 U.S.C., Appendix 1, 10(a)). This document is intended to notify the general public of its opportunity to attend.

DATES: The Panel will meet Sunday, September 11 from 7 p.m. to 10 p.m. and Monday, September 12 from 9 a.m. to 5 p.m.

ADDRESS: National Institute of Education, Room 823, 1200 19th Street NW., Washington, D.C. 20208.

FOR FURTHER INFORMATION CONTACT:

Mr. John O'Brien, Laboratory and Center, Task Force, National Institute of Education, 1200 19th Street NW., Washington, D.C. 20208.

The Panel for the Review of Laboratory and Center Operations was established under the provisions of Section 403 of the Education Amendments of 1976. The Panel is directed to:

(A) Review and prepare recommendations on initial long-range plans of the laboratories and centers.

(B) Review the operations of the laboratories and centers receiving assistance and make recommendations for the