(2), (3), or (4) above. Clinical studies demonstrating substantial evidence of effectiveness will not be required, but a clinical study demonstrating that the combination product does not cause hepatic injury will be required. Such a study may not be required if it is demonstrated by clinical evidence supplied from the literature that the combination is non-toxic. In vitro dissolution rate studies are required as part of the application. In vivo demonstration of bioavailability shall be required of products which fail to achieve adequate dissolution.

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 National Center for Drugs and Biologics (see 21 CFR 5.70 and 47 FR 26913 published in the Federal Register of June 22, 1982).

Dated: July 1, 1982.

Harry M. Meyer, Jr.,

Director, National Center for Drugs and Biologics.

[FR Doc. 82-21739 Filed 8-9-82; 8:45 am]

BILLING CODE 4160-01-M

[Docket No. 80N-0382; DESI Nos. 64, 6340, 7337, 8658, 10996, and 11792]

Prescription and Over-the-Counter Drug Products Containing Phenacetin; Opportunity for Hearing on Proposal To Withdraw Approval of New Drug Applications

AGENCY: Food and Drug Administration (FDA).

ACTION: Notice.

SUMMARY: This notice proposes to withdraw approval of new drug applications for both prescription and over-the-counter (OTC) drugs containing phenacetin due to its high potential for abuse and its unfavorable benefit-to-risk ratio when incorporated in analgesic mixtures which are then subjected to excessive chronic use. All drug products containing phenacetin are subject to this notice. Manufacturers must reformulate their products to delete phenacetin or replace it with another analgesic on or before August 10, 1983. Thereafter the marketing of any drug product containing phenacetin that is not the subject of a pending hearing request will be regarded as unlawful.

DATES: Hearing requests due on or before September 9, 1982.

ADDRESSES: Communications in response to this notice should be identified with Docket No. 80N-0382, directed to the attention of the appropriate office named below, and addressed to the Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.

Supplements to full new drug applications (identify with NDA number): Division of Neuropharmacological Drug Products (HFD–120), Rm. 10B–34 (or Division of Surgical-Dental Drug Products (HFD–160), Rm. 18B–03, National Center for Drugs and Biologics.

Supplements to abbreviated new drug applications (identify with ANDA number): Division of Generic Drug Monographs (HFD–530), National Center for Drugs and Biologics.

Requests for Hearing (identify with Docket Number appearing in the heading of this notice): Dockets Management Branch (HFA–305), Rm. 4–62.

Requests for guidelines or information on conducting dissolution tests and bioavailability studies: Division of Biopharmaceutics (HFD–520), National Center for Drugs and Biologics.

Questions about phenacetic substitutes and whether a reformulated product is identical, similar, or related to a drug product evaluated by the Drug Efficacy Study Implementation (DESI) review: Division of Drug Labeling Compliance (HFD–310), National Center for Drugs and Biologics, Rm. 9B–28 (301–443–3750).

FOR FURTHER INFORMATION CONTACT: Herbert Gerstenzang, National Center for Drugs and Biologics (HFD–32), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857; 301–443–3650.

SUPPLEMENTARY INFORMATION:

Background

Phenacetin, an ingredient in prescription and OTC drug products, has been widely used as an analgesic for over 80 years. It is usually used in combination with other analgesic ingredients; it is virtually never used as a single-ingredient drug product. Analgesic mixtures containing phenacetin when used chronically and excessively can result in severe and irreversible toxic effects. Phenacetin's history of abuse from its misuse and prolonged use led FDA in 1964 to require a warning statement in the labeling of all phenacetin-containing preparations. See 21 CFR 201.309.

In 1977, the FDA Advisory Review Panel on Over-the-Counter Internal Analgesic and Antirheumatic Products classified phenacetin as not safe for OTC use as an analgesic because of the high potential for abuse, the high potential for harm to the kidneys from phenacetin-containing mixtures, and the possibility of hemolytic anemia and methemoglobinemia resulting from abuse. In arriving at its conclusions regarding the safety of phenacetin, the Panel considered documented evidence showing:

1. That the central nervous system effects of phenacetin appear to be a major factor in the chronic abuse of combinations containing this drug. Several authors of the medical literature reviewed noted the habituation potential of phenacetin-containing combinations.

2. An association between excessive chronic ingestion of phenacetin-containing analgesics and life-threatening urinary tract and kidney disease (renal papillary necrosis, nonobstructive interstitial nephritis, calcification), and cancer of the kidney and bladder.

A thorough review of the literature on the relationship between phenacetin and severe renal disease was made by the Panel and submitted for outside statistical evaluation. Numerous experts appeared before the Panel. In addition, the Panel collected new information from a variety of sources including kidney dialysis centers and regulatory agencies of other countries. The Panel report states in part at 42 FR 35425:

"In the opinion of the Panel, the evidence relating phenacetin to severe renal disease now derives from a world body of published reports so numerous and varied in design that the possibility of coincidental association is negligible and requires that phenacetin be removed from the OTC drug market.

"There is a view set forth in material submitted to the Panel that phenacetin should not be singled out as the causative agent in analgesic combination products because other agents in analgesic combinations, such as aspirin or acetaminophen, have been shown to produce kidney damage when used alone in man and animals; whereas phenacetin alone has rarely been shown to produce kidney damage in man. . . . The Panel does not agree with this argument because there are now thousands of reported cases of kidney disease associated with the use of phenacetin-containing mixtures, while there are probably no more than ten well-documented cases of analgesic-induced kidney disease in the world literature that can be definitively associated with abuse of all other single-agent products or combination analgesic products not involving phenacetin, even though these products are extensively used throughout the world. The Panel has discussed the adverse effects of

aspirin on the kidney elsewhere in this document. * * *

"From the point of view of safety of phenacetin, whether it causes kidney disease itself, augments effects of other active ingredients or increases the use of other nephrotoxic agents, it is the Panel's opinion that prolonged excessive ingestion of any common analgesic product containing phenacetin will significantly increase the probability of serious kidney disease and premature death. These levels and duration of ingestion, far exceeding label directions for use of such analgesic mixtures, are indicative of a serious potential for abuse problem that the Panel believes is associated with CNS effects of phenacetin and other components of such mixtures. This is especially true for powder formulations.

"Phenacetin is virtually never used as a single agent in the U.S. or any other country. It is almost always commercially available and used only in combinations containing other analgesic compounds. Obviously, since the actual use of phenacetin as a single entity is rare, it could not be expected that renal disease resulting from its use alone would occur or be reported. It should be noted though that at least one case allegedly involving only phenacetin has been reported * * *. Although epidemiological or experimental studies on the effects of phenacetin alone in producing renal disease in man are not available or feasible, several other types of evidence indicate the major involvement of phenacetin in analgesic-induced renal disease.

"In several major industrialized countries, where kidney disease induced by analgesic abuse has been a problem, many analgesic mixtures have been involved. Phenacetin has been the common denominator of analgesic products responsible for the problem. In the U.S., available data also indicate that phenacetin-containing products are invovled in almost all reported cases of analgesic-induced kidney disease * * *.

"In addition to phenacetin being involved qualitatively as the common denominator, data from several countries show similar quantitative relationships between the dose of phenacetin required to produce a given degree of kidney injury or incidence of kidney disease, irrespective of the dose of other agents involved * * *.

"Retrospective case control studies indicate that total doses of 2 to 4 kg phenacetin over a period of about 10 years would result in approximately a 70 percent probability of renal papillary necrosis. The probability of death due to kidney failure in patients with degeneration of the part of the kidney affected by phenacetin is about 30 to 40 percent. This incidence appears to be similar for all mixtures of phenacetin regardless of whether they contain aspirin, antipyrine, or caffeine.

"Several different types of studies consistently suggest temporal and dose relationships between phenacetin ingestion and renal dysfunction. In the opinion of the Panel, and consulting reviewers, studies following changes in renal function in the same individual or groups of individuals when phenacetin is removed, replaced, or readministered provide strong evidence for a direct causal effect. Followup studies in countries after complete removal of phenacetin from nonprescription use have shown a decrease in the incidence of kidney damage associated with analgesic abuse as will be discussed later in this document * * *. This not only supports the assumption of causality but also the conclusion that removal from OTC drug status would be beneficial. Data collected from kidney dialysis units in the U.S. and previous autopsy studies suggest the incidence of analgesic-induced kidney disease to be significantly high to warrant the Panel's action to recommend restriction of this drug from the OTC drug market * * *.

"The Panel further believes that these data provide the same early warning indications seen in other countries just before analgesic-induced kidney disease was diagnosed as a major public health problem. The 'lag time' between several initial diagnoses of analgesic-induced kidney disease and the realization that in fact the problem was widespread is what most concerns the Panel. While there are not large numbers of cases of analgesic-induced kidney disease being presently reported in the U.S., the Panel believes that if the medical community were aware of this problem and looked for this type of kidney disease, the incidence of analgesic-induced kidney disease would in fact be found to be a major public health problem in the U.S."

More detailed examination and documentation of the data supporting these Panel conclusions are contained in the Panel's report and proposed monograph for OTC Internal Analgesic, Antipyretic and Antirheumatic Products (Ref. 1) published in the Federal Register of July 8, 1977 (42 FR 35346) on pages 35424–35434.

The central nervous system effects of phenacetin in combination products have been further reported in recent years in experimental studies (Ref. 41) and in historical surveys (Refs. 42, 43) where both in the United States and in Europe phenacetin-containing combination products have been used for nonanalgesic indications.

Although attempts have been made to define the prevalence of analgesic abuse, it has been impossible so far to arrive at a generalized assessment. Real differences exist in the prevalence between countries and between different sections of individual countries, e.g., the United States and Australia (Refs. 42 through 46). The public health problems are primarily those secondary to chronic ingestion and although analgesic abuse leads to multiorgan dysfunction, it is primarily the renal disease that is of public health importance. It is estimated that in some areas of the United States "20 percent of patients with interstitial nephropathy had ingested large quantities of analgesic mixtures and that this consumption appeared to be the primary cause of their renal disease" (Ref. 45).

The adverse effects of chronic high doses of phenacetin-containing analgesic combination products discussed above and in the OTC Panel report have also been documented in recent medical literature (Refs. 41 through 45, 47 through 49). While experimental data from animal studies (Ref. 44) suggest that aspirin is more potent than phenacetin in producing renal papillary necrosis in animals, when the drugs are taken together the incidence of renal lesions is greater than with aspirin alone. Analgesic nephropathy is rare in humans who have abused aspirin alone, presumably because of the lesser toxic propensities of aspirin in man and less potential for abuse of the single ingredient. Although analgesic nephropathy occurs in patients with rheumatoid arthritis, the incidence is not high, and in almost all reported series has been limited to those patients who have taken combination analgesics containing phenacetin and not to those patients who have taken large quantities of aspirin alone (Ref. 46). Kincaid-Smith (Ref. 42) states that dosage may account for the fact that patients with rheumatoid arthritis who take aspirin for prolonged periods do not have a high incidence of analgesic nephropathy. That is, although they take large amounts of aspirin by conventional standards, the amounts are often less than those taken by analgesic abusers. Kincaid-Smith further states that when serious analgesic nephropathy is found in patients with rheumatoid arthritis they have almost always abused drug combinations.

It has also been suggested by Nanra et al. (Ref. 44) that removal of phenacetin from combination analgesics does not lower the incidence of analgesic nephropathy. This is based on a study in Australia of two consecutive groups of

patients who had exclusively abused either a product containing aspirin, phenacetin, and caffeine or a product containing aspirin, salicylamide, and caffeine. The authors concluded that the absence of phenacetin from this one product over an eight-year period did not appear to influence the frequency of renal insufficiency in patients. However, the pattern of drug ingestion in these patients was not validated in any manner other than by patient history, and the free availability of phenacetin in other OTC products throughout the period of the study raises issues of validity of these findings. This is in contrast to the experience in Canada, Denmark, and Sweden (Refs. 43, 46, 50) where removal of phenacetin from all combination analgesic products has resulted in a significant decline in analgesic nephropathy as measured by sensitive indices (Refs. 47, 49). There appear to be true differences between analgesic nephropathy as it occurs in Australia and as it occurs in other countries. Evidence of this is Australia's high frequency (25 percent) of end stage renal disease associated with analgesic nephropathy compared to 3.1 percent in Europe. This difference was also noted and discussed by the OTC Panel (Ref. 1).

Due to FDA's increasing concern about the toxicity of phenacetin, the agency requested its Peripheral and CNS Drugs Advisory Committee to evaluate the data on the safety and effectiveness of phenacetin in prescription analgesic combination products. At its meeting of February 13–14, 1978, the Committee concluded that a statement on the association of phenacetin with renal damage should be required in the labeling of such products, but the committee did not recommend that phenacetin be removed from the prescription drug market. On November 20, 1978, FDA wrote to NDA holders for prescription products that contained phenacetin, asking them to add a boxed warning statement to the labeling highlighting the association of large doses of phenacetin for long periods with severe kidney disease and with cancer of the kidney, and to add a statement to the Warnings section concerning kidney disease associated with phenacetin. Many firms have already revised their labeling to include these warnings. Since August 7, 1964, warning statements on the hazards of long-term use of phenacetin have been required in the labeling of phenacetin-containing products under 21 CFR 201.309.

Although the evidence linking abuse of analgesics to cancer of the kidney was not reviewed by the Peripheral and CNS Drugs Advisory Committee in 1978, several reports implicating long-term use of phenacetin-containing products with cancer of the kidney and urinary bladder were reviewed by both the OTC Panel (Ref. 1) and FDA (Refs. 21 through 40). FDA later reviewed additional medical literature, notably the 1978 Bengtsson report (Ref. 40) which states that over 100 cases of uro-epithelial cancers have been reported in users of phenacetin-containing analgesics. In 1980, the first epidemiologic study of analgesic nephropathy and transitional cell carcinoma of the urinary tract was reported from the United States by Gonwa et al. (Ref. 51). The findings here were consistent with the previous epidemiologic studies from Europe and implicate analgesic abuse, particularly of phenacetin, as being carcinogenic.

The Director of the National Center for Drugs and Biologics has reevaluated the conclusions of the Advisory Review Panel on Over-the-Counter Internal Analgesic and Antirheumatic Products, the Peripheral and CNS Drugs Advisory Committee, and the evidence available to the agency as discussed above and concludes that because the high potential for abuse of phenacetin-containing products may lead to excessive ingestion, producing a clinical syndrome characterized by serious kidney disease and premature death, the risks from use of such combination drug products outweigh any benefit and therefore they cannot be considered safe. The medical literature (Ref. 44) also reports that this clinical syndrome is characterized by gastrointestinal symptoms with peptic ulcerations in 35 percent of patients, anemia in 60–90 percent, hypertension in 15–70 percent, ischemic heart disease in 35 percent, pigmentation, psychiatric disorders, and possible effects on pregnancy. Although phenacetin is not unique in its ability to cause nephropathy, its central nervous system properties make it likely that analgesic combination products containing phenacetin will be abused. Because of the availability of other safe and effective analgesics both for prescription and OTC use, consumers would not be deprived of useful analgesic products.

Proposed Action

The Food and Drug Administration is charged with assuring that drugs are safe and effective for their intended use. The statutory framework anticipates that new information on the safety of marketed drugs may require that FDA withdraw certain drug products from the market or cause certain ingredients to be deleted from drug products, or prescribe changes in their labeling to reveal limitations on use, or to warn of previously unanticipated hazards. See 21 U.S.C. 352 and 355. In accordance with the Federal Food, Drug, and Cosmetic Act, the Director is now proposing to withdraw approval of all new drug applications for products containing phenacetin. However, the agency has determined that most of the products that contain phenacetin can be reformulated adequately by either deleting phenacetin or by replacing it with another analgesic whose safety and effectiveness is well established, thereby permitting reformulation to safe and effective products without the need to conduct safety and effectiveness studies. Therefore, these products as reformulated may continue to be available to consumers without marketing disruption. Many products that contained phenacetin have already been reformulated; several manufacturers have expressed a desire to reformulate their products and are awaiting FDA guidelines. In many other countries phenacetin has already been removed from the market without causing problems for consumers or manufacturers.

This notice applies not only to the particular phenacetin-containing drug products listed below, but also to any phenacetin-containing drug product that is the subject of a new drug application (NDA) approved either before or after the Drug Amendments of 1962 and to any other drug products containing phenacetin, whether or not they are the subject of approved NDA's. OTC drug products containing phenacetin previously deferred to the OTC review (37 FR 9464) are no longer deferred and are subject to this notice. Therefore, OTC drug products containing phenacetin will not be subject to the full OTC rule making procedure set forth in § 330.10 (21 CFR 330.10).

I. Prescription Drug Products Containing Phenacetin.

A. The following products contain aspirin 200 mg, butalbital 50 mg, caffeine 40 mg, and phenacetin 130 mg.

1. NDA 17–534; Fiorinal Tablets and Capsules; Sandoz Pharmaceuticals, P.O. Box 11, Route 10, E. Hanover, NJ 07936.

2. ANDA 85–441; APC with Butalbital Tablets; Zenith Laboratories, Inc., 140 Le Grand Ave., Northvale, NJ 07647.

3. ANDA 86–162; Butalbital with APC Tablets; West-Ward, Inc., 465 Industrial Way West, Eatontown, NJ 07724.

4. ANDA 86–231; A.P.C. with Butalbital Capsules; Chelsea Laboratories, Inc., 428 Doughty Blvd., Inwood, NY 11696.

5. ANDA 86-237; A.P.C. with Butalbital Tablets; Chelsea Laboratories, Inc.

6. ANDA 86-398; Butal Compound Tablet; Cord Laboratories, Inc., 2555 West Midway Blvd., Broomfield, CO 80020.

7. ANDA 86-432; Butal Compound Capsule; Cord Laboratories, Inc.

8. ANDA 86-710; A.P.C. with Butalbital Tablets; Purepac Pharmaceutical Co., 200 Elmora Ave., Elizabeth, NJ 07207.

9. ANDA 86-986; Lanorinal Tablets; Lannett Co., Inc., 900 State Rd., Philadelphia, PA 19136.

10. ANDA 86-996; Lanorinal Capsules; Lannett Co., Inc.

11. ANDA 87-048; Butalbital with APC Tablets; Generic Pharmaceutical Corp., 433 Commerical Ave., Palisades Pk., NJ 07650.

12. ANDA 87-279; Butalbital with APC Tablets; Premo Pharmaceutical Laboratories, Inc., 111 Leuning St., South Hackensack, NJ 07606.

B. The following products contain aspirin 227 mg, caffeine 32.4 mg, phenacetin 162 mg, and propoxyphene hydrochloride 65 mg.

1. NDA 10-996; Darvon Compound 65 Capsules; Eli Lilly & Co., Box 618, Indianapolis, IN 46206.

2. ANDA 80-044; Propoxyphene Compound 65 Capsules; Federal Pharmacal, Inc., P.O. Box Q, Kingshill St., St. Croix, VI 00850.

3. ANDA 80-882; ICN 65 Compound Capsules; ICN Pharmaceuticals, Inc., 5040 Lester Rd., Cincinnati, OH 45213.

4. ANDA 83-077; Propoxyphene Compound 65 Capsules; Zenith Laboratories, Inc.

5. ANDA 83-072; Propoxyphene Compound 65 Capsules; Mylan Pharmaceuticals, Inc., P.O. Box 4293; Morgantown, WV 26505.

6. ANDA 83-086; Dolene Compound-65 Capsules; Lederle Laboratories, Pearl River, NY 10965.

7. ANDA 83-101; Propoxyphene Compound 65 Capsules; Cord Laboratories.

8. ANDA 83-106; SK-Propoxyphene APC Capsules; Smith Kline & French Laboratories, 1500 Spring Garden St., Philadelphia, PA 19101.

9. ANDA 83-230; Propoxyphene Compound 65 Capsules; Parke Davis, Division of Warner-Lambert Co., 201 Tabor Rd., Morris Plains, NJ 07950.

10. ANDA 83-530; Propoxyphene Compound 65 Capsules; Purepac Pharmaceutical Co.

11. ANDA 83-681; Propoxyphene HCl with A.P.C. Capsules; Richyln Laboratories, 3725 Castor Ave., Philadelphia, PA 19124.

12. ANDA 83-701; Propoxyphene Compound 65 Capsules; Towne Paulsen & Co., Inc., 140 E. Duarte Rd., Monrovia, CA 91016.

13. ANDA 83-737; Repro Compound 65 Capsules; Reid-Provident Laboratories, Inc., 640 10th St., Atlanta, GA 30318.

14. ANDA 83-968; Propoxyphene HCl with A.P.C. Capsules; Mylan Pharmaceuticals, Inc.

15. ANDA 84-190; Propoxyphene Compound 65 Capsules; Anabolic, Inc., 17802 Gillette Ave., Irvine, CA 92664.

16. ANDA 84-207; Propoxyphene HCl Compound 65 Capsules; Philips Roxane Laboratories, Inc., 330 Oak St., Columbus, OH 43216.

17. ANDA 84-249; Propoxyphene HCl with A.P.C. Capsules; Abbott Laboratories, Inc., 14th & Sheridan Rd., N. Chicago, IL 60064.

18. ANDA 84-553; SK-65 Compound Capsules; Smith Kline & French Laboratories.

19. ANDA 85-732; Propoxyphene Compound 65 Capsules; Chelsea Laboratories.

20. ANDA 86-488; Propoxyphene Compound 65 Capsules; Premo Pharmaceutical Laboratories, Inc.

21. ANDA 87-142; Dolene Compound-65 Capsules; Lederle Laboratories.

C. NDA 10-996; Darvon Compound Capsules containing aspirin 227 mg, caffeine 32.4 mg, phenacetin 162 mg, and propoxyphene hydrochloride 32 mg; Eli Lilly & Co.

D. NDA 16-864; Darvo Comp-N 50 Tablets containing aspirin 227 mg, caffeine 32.4 mg, phenacetin 162 mg, and propoxyphene napsylate 50 mg; Eli Lilly & Co.

E. NDA 16-864; Darvo Comp-N 100 Tablets containing aspirin 227 mg, caffeine 32.4 mg, phenacetin 162 mg, and propoxyphene napsylate 100 mg; Eli Lilly & Co.

F. NDA 7-337; Percodan Tablets containing aspirin 224 mg, caffeine 32 mg, oxycodone hydrochloride 4.5 mg, oxycodone terephthalate 0.38 mg, and phenacetin 160 mg; Endo Laboratories, Inc., 1000 Stewart Ave., Garden City, NJ 11530.

G. NDA 7-337; Percodan-Demi Tablets containing aspirin 224 mg, caffeine 32 mg, oxycodone hydrochloride 2.25 mg, oxycodone terephthalate 0.19 mg, and phenacetin 160 mg; Endo Laboratories, Inc.

H. NDA 10-894; Zactirin Compound-100 Tablets containing aspirin 227 mg, caffeine 32.4 mg, ethoheptazine citrate 100 mg, and phenacetin 162 mg, Wyeth Laboratories, Inc., P.O. Box 8299, Philadelphia, PA 19101.

I. NDA 11-536; Kryl Tablets containing ascorbic acid 100 mg, aspirin 230 mg, isothipendyl hydrochloride 4 mg, phenacetin 160 mg, and phenylephrine hydrochloride 5 mg; Ayerst Laboratories, 685 Third Ave., New York, NY 10017.

J. NDA 12-365; Soma Compound Tablets containing caffeine 32 mg, carisoprodol 200 mg, and phenacetin 160 mg, Wallace Laboratories, Half Acre Rd., Cranbury, NJ 08512.

K. ANDA 87-042; Carisoprodol Compound Tablets containing caffeine 32 mg, carisoprodol 200 mg, and phenacetin 160 mg, Bolar Pharmaceutical Co., Inc., 130 Lincoln St., Copiaque, NY 11726.

L. NDA 12-365; Soma Compound with Codeine Tablets containing caffeine 32 mg, carisoprodol 200 mg, codeine phosphate 16 mg, and phenacetin 160 mg; Wallace Laboratories.

M. NDA 13-416; Norgesic Tablets containing aspirin 225 mg, caffeine 30 mg, orphenadrine citrate 25 mg, and phenacetin 160 mg; Riker Laboratories, Inc., 19901 Nordhoff St., Northridge, CA 91324.

N. NDA 13-416; Norgesic Forte Tablets containing aspirin 450 mg, caffeine 60 mg, orphenadrine citrate 50 mg, and phenacetin 320 mg; Riker Laboratories, Inc.

O. NDA 16-109; Sinubid Sustained Release Tablets containing acetaminophen 300 mg, phenacetin 300 mg, phenylpropanolamine hydrochloride 100 mg, and phenyltoloxamine citrate 66 mg; Warner-Lambert Co., 201 Tabor Rd., Morris Plains, NJ 07950.

II. OTC Drug Products Containing Phenacetin (some of these products have been discontinued and are not being marketed.)

A. That part of NDA 6-412 pertaining to Decapryn S with APC containing aspirin 230 mg, caffeine 30 mg, phenacetin 150 mg, and doxylamine succinate 6 mg or 12 mg; Merrell-Dow Pharmaceutical Inc., P.O. Box 15260, Cincinnati, OH 45215.

B. That part of NDA 6-412 pertaining to Decapryn with APC containing aspirin 230 mg, caffeine 30 mg, phenacetin 150 mg, and doxylamine 6 mg or 12 mg; Merrell-Dow Pharmaceuticals Inc.

C. That part of NDA 6-921 pertaining to Coricidin Tablets containing aspirin 3.5 gr, caffeine 0.5 gr, chlorpheniramine maleate 2 mg, and phenacetin 2.5 gr; Schering Corp., Galloping Hill Rd., Kenilworth, NJ 07033.

D. Those parts of NDA 6-303 and 7-026 pertaining to Thephorine Tablets containing aspirin 160 mg, caffeine 15 mg, phenacetin 160 mg, and phenindamine tartrate 10 mg; Hoffmann-LaRoche, Inc., Roche Park, Nutley, NJ 07110.

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E. That part of NDA 7-018 pertaining to Thenfadil Compound Tablets containing aspirin 180 mg, caffeine 15 mg, phenacetin 120 mg, and thenyldiamine maleate 6 mg; Winthrop Laboratories, 90 Park Ave., New York, NY 10016.

F. NDA 7-352; Hista-Pac Tablets containing aspirin 3.5 gr, caffeine 0.5 gr, phenacetin 2.5 gr, and pyrilamine maleate 25 mg; Hance Bros. & White Co., 442 North 12th St., Philadelphia, PA 19123.

G. NDA 7-812; Inhiston-APC Tablets containing aspirin 3.5 gr, caffeine 0.5 gr, phenacetin 2.5 gr, and phenyramine maleate 10 mg; Plough, Inc., P.O. Box 377, Memphis, TN 38151.

H. NDA 8-528; Bristamine-APC containing aspirin 210 mg, caffeine 30 mg, phenacetin 150 mg, and phenyltoloxamine 25 mg; Bristol Laboratories, P.O. Box 657, Syracuse, NY 13201.

I. NDA 11-292; Cardui Tablets containing pamabrom 25 mg, phenacetin 125 mg, and salicylamide 200 mg; Chattanooga Medicine Co., 1715 West 38th St., Chattanooga, TN 37409.

J. NDA 11-849; Pamprin Tablets containing pamabrom 25 mg, phenacetin 125 mg, pyrilamine maleate 12.5 mg, and salicylamide 250 mg; Chattem Chemicals, 1715 West 38th St., Chattanooga, TN 37409.

K. NDA 11-922; Carbetapentane Citrate with SPC Capsules containing caffeine 0.5 gr, carbetaphetane citrate 12.5 mg, phenacetin 1.25 gr, and salicyamide 3.5 gr; USV Laboratories, 1 Scarsdale Rd., Tuckahoe, NY 10707.

Accordingly, all drug products that contain phenacetin are regarded as new drugs (21 U.S.C. 321(p)) and are subject to the requirements of this notice.

Opportunity for Hearing

Therefore, notice is given to the holders of the new drug applications for products containing phenacetin and to all other interested persons that the Director of the National Center for Drugs and Biologics proposes to issue an order under section 505(e) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(e)), withdrawing approval of the new drug applications (or if indicated above, those parts of the applications providing for the drug products listed above) and all amendments and supplements thereto because new evidence of clinical experience, not contained in such applications or not available to the Director until after such applications were approved, evaluated together with the evidence available to the Director when the applications were approved, shows that such drugs are not shown to be safe for use under the conditions of use on the basis of which the applications were approved.

This notice of opportunity for hearing applies not only to new drug application holders (named above), but to all persons who manufacture or distribute a drug product, whether prescription or over-the-counter, that contains phenacetin. It is the responsibility of every drug manufacturer or distributor to review this notice of opportunity for hearing to determine whether it covers a drug product that the person manufactures or distributes. Such person may request an opinion of the applicability of this notice to a specific drug product by writing to the Division of Drug Labeling Compliance (address given above).

In accordance with section 505 of the act (21 U.S.C. 355) and the regulations promulgated under it (21 CFR Parts 310, 314), the applicants and all other persons subject to this notice including drug manufacturers of over-the-counter products containing phenacetin are hereby given an opportunity for a hearing to show why approval of the new drug applications should not be withdrawn and an opportunity to raise, for administrative determination, all issues relating to the legal status of drug products containing phenacetin.

An applicant or any other person subject to this notice who decides to seek a hearing, shall file (1) on or before September 9, 1982, a written notice of appearance and request for hearing, and (2) on or before October 12, 1982, the data, information, and analyses relied on to justify a hearing, as specified in 21 CFR 314.200. Any other interested person may also submit comments on this notice. The procedures and requirements governing this notice of opportunity for hearing, a notice of appearance and request for hearing, submission of data, information, and analyses to justify a hearing, submission of other comments, and the granting or denial of hearing, are contained in 21 CFR 314.200.

The failure of an applicant or any other person subject to this notice to file a timely written appearance and request for hearing as required by 21 CFR 314.200 constitutes an election by the person not to make use of the opportunity for a hearing concerning the action proposed with respect to the product and constitutes a waiver of any contentions concerning the legal status of any such drug product. Any such drug product 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 new drug application 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 of Food and Drugs will enter summary judgment against the person(s) who requests the hearing, making findings and conclusions, denying a hearing. See 21 CFR 314.200(g).

All submissions under this notice must be filed in four copies. Such submissions, except for data and information prohibited from public disclosure under 21 U.S.C. 331(j) or 18 U.S.C. 1905, may be seen in the office of the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

Guidelines for Reformulation

The Director has determined that most phenacetin-containing combination products currently being marketed can be reformulated by deleting phenacetin or by replacing phenacetin with another analgesic. Manufacturers will be given until August 10, 1983, to reformulate their products. Reformulation of an OTC drug product containing phenacetin must be in accord with the provisions of any applicable OTC drug final monograph. Before an applicable OTC drug final monograph is published, manufacturers of such OTC drug products may reformulate either by deleting phenacetin or by replacing phenacetin with other analgesic ingredients, provided the following conditions are met. The reformulation does not result in a product containing a combination of ingredients not previously marketed in this country; and it does not result in a product containing (1) an active ingredient limited to prescription use on or after May 11, 1972, or (2) an active ingredient present at a dosage level higher than that available in any OTC drug product on December 4, 1975, and unless the ingredient and/or dosage level (single unit or total daily dosage) is classified in a proposed or tentative final monograph in Category I.

Phenacetin-containing prescription drug products that are the subject of an

approved full or abbreviated new drug application may be reformulated without prior FDA approval by either deleting phenacetin or replacing phenacetin with another analgesic ingredient as follows: (1) Because the data establishing the safety and effectiveness of the analgesics aspirin and acetaminophen are well-known, phenacetin in combination products containing one of these analgesics should be replaced on a milligram-for-milligram basis with aspirin or acetaminophen, whichever analgesic ingredient is already in the product. (2) If both of the above analgesics are in a product, then either one or both of the analgesics present can be used to replace the phenacetin on a milligram-for-milligram basis (i.e., the total milligram amount of the analgesics added must be equal to the milligram amount of phenacetin deleted). Clinical studies demonstrating the safety and effectiveness of the reformulated product are not required. If reformulated as above these products may be marketed before FDA approves a supplemental application, according to the procedure provided by 21 CFR 314.8 (d) and (e).

A manufacturer may not reformulate a phenacetin-containing prescription drug product that is the subject of an approved full or abbreviated new drug application by substituting for phenacetin another analgesic ingredient not now in the drug product unless a supplemental application is first approved. Clinical studies will not be required for a reformulated product in which either aspirn or acetaminophen is substituted for phenacetin, except when acetaminophen is substituted for phenacetin and the product contains a known or potential inducer of hepatic enzymes; then a liver toxicity study will be required. An applicant may not be required to conduct such a study if it is demonstrated by clinical evidence supplied from the literature that the combination is non-toxic. For the prescription drug products listed in this notice, the only products of which the agency is aware that would require such evidence on liver toxicity (because they do not already contain aspirin or acetaminophen which can be increased to replace phenacetin) are products containing carisoprodol. If the phenacetin ingredient is in carisoprodol-containing products is replaced with acetaminophen, then supplements to full new drug applications or full new drug applications will be required.

Reformulation of a product that is now the subject of an approved ANDA by substituting for phenacetin an analgesic other than aspirin or acetaminophen will require a full approved NDA if FDA has not made a determination that an ANDA is acceptable. Because the Director is allowing manufactures 1 year in which to reformulate their products, early submission of a supplement or full new drug application requiring premarketing approval will provide a better opportunity for the applicant to obtain approval of the reformulated product in time to avoid interruption in its marketing.

Products that are subject to the drug efficacy study (DESI) program will continue to be subject to the requirements and conditions of the DESI program when the products are reformulated to delete phenacetin or to replace it with another analgesic. Reformulation of a phenacetin-containing prescription drug product subject to DESI for which a final effectiveness determination has been made must be in accordance with the applicable DESI notice. For example butalbital-analgesic combination products containing phenacetin are subject to DESI 64 which appears elsewhere in this issue of the Federal Register. A number of phenacetin-containing products also are in that part of the DESI program for which a final effectiveness determination has not yet been made. The Director advises that reformulation in accord with this notice will not alter any interim classifications of these drug products as less-than-effective.

Any phenacetin-containing prescription drug product that is not the subject of an approved NDA may be reformulated in accord with the same requirements as set forth for a prescription product that is the subject of an NDA. However, the reformulated product may result in a product that requires an approved NDA or ANDA prior to marketing. Inquiries as to the new drug status of a product should be sent to the Division of Drug Labeling Compliance (address given above).

The supplemental new drug applications, abbreviated new drug applications, or full new drug applications submitted for reformulated drug products as required by this notice are to include in vitro dissolution rate studies with the methods provided for in the guidelines on conducting dissolution tests and bioavailability studies, which are available from the Division of Biopharmaceutics at the address given above. In vivo demonstration of bioavailability shall be required of all products which fail to achieve adequate dissolution.

Any change in the formulation of a drug product required by this notice is subject to the requirements of 21 CFR 207.30 (drug listing amendment).

The Director intends to publish a notice withdrawing approval of those parts of the new drug applications that provide for products containing phenacetin, except for those products that are the subject of a hearing request, by October 12, 1982. The effective date of the withdrawal notice will be August 10, 1983. Therefore, any drug product containing phenacetin initially introduced or initially delivered for introduction into interstate commerce after August 10, 1983, except for a drug still the subject of a hearing request, will be considered misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 352) and a new drug within the meaning of section 201(p) for which an approved new drug application under section 505 of the act (21 U.S.C. 355) and Part 314 of the regulations is required for marketing. In the absence of an approved new drug application, any such drug product initially introduced or initially delivered for introduction into interstate commerce after August 10, 1983 will be subject to regulatory action. The agency concludes that although phenacetin poses an unfavorable benefit-to-risk ratio when incorporated into analgesic mixtures, a recall of phenacetin products is not warranted. Further, many firms have already reformulated their products and the agency expects that many other firms will reformulate their products as a result of the publication of this notice.

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Reprints of the above references have been placed on file with the Dockets Management Branch (address given above) and may be seen between 9 a.m. and 4 p.m., Monday through Friday.

This notice is issued under the Federal Food, Drug, and Cosmetic Act (sec. 505, 52 Stat. 1052–1053, as amended (21 U.S.C. 355)) and under the authority delegated to the Director of the National Center for Drugs and Biologics (see 21 CFR 5.82 and 47 FR 26913 published in the Federal Register of June 22, 1982).

Dated: July 1, 1982.

Harry M. Meyer, Jr.,

Director, National Center for Drugs and Biologics.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Statement of Organization, Functions, and Delegations of Authority; Food and Drug Administration

Part H, Chapter HF (Food and Drug Administration) of the Statement of Organization, Functions, and Delegations of Authority for the Department of Health and Human Services (35 FR 3685–92, February 25, 1970, as amended in pertinent part at 43 FR 16418–19, April 18, 1978) is amended to reflect the consolidation of the Office of Public Affairs and the Office of Legislative Affairs into a new Office of Legislation and Information. This reorganization will provide a single release point for FDA information to Congress and the media thereby ensuring better coordination between