Dated: September 24, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

[FR Doc. 80-29966 Filed 9-25-80; 8:45 am]

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21 CFR Part 348

[Docket No. 78N-0301]

External Analgesic Drug Products for Over-the-Counter Human Use; Reopening of the Administrative Record

AGENCY: Food and Drug Administration.

ACTION: Reopening of administrative record.

SUMMARY: This notice advises that the Food and Drug Administration (FDA) is reopening the administrative record for over-the-counter (OTC) external analgesic drug products to allow for consideration of recommendations on camphor-containing drug products that have been received from the Advisory Review Panel on OTC Miscellaneous External Drug Products.

DATES: Comments by November 25, 1980, and reply comments by December 26, 1980.

ADDRESS: Written comments to the Hearing Clerk (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: The Food and Drug Administration (FDA) published the report and proposed monograph of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel) on OTC external analgesic drug products for human use on December 4, 1979 (44 FR 69768). Interested persons could have filed written comments regarding this proposal by March 6, 1980, and comments replying to comments by April 3, 1980. After the closing of the comment period following publication of the panel report, new data and information may be submitted for inclusion into the administrative record only through a petition to reopen the administrative record.

The Topical Analgesic Panel concluded that camphor is safe and effective for use as an OTC external analgesic at a concentration of 0.1 to 3.0 percent when labeled for use as a topical analgesic, anesthetic, and antipruritic. Additionally, this panel recommended that camphor was safe and effective at concentrations higher than 3 percent, but not exceeding 11 percent, when labeled for use as a topical counterirritant. Following the publication of this panel's recommendations on camphor, the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) also reviewed camphor. The Miscellaneous External Panel, however, concluded that OTC products containing greater than 2.5 percent camphor have a low benefit-to-risk ratio and recommended that camphor be limited in OTC drug products for external use to less than 2.5 percent. The Miscellaneous External Panel also recommended that the quantity of camphor in a package be limited to a total of 360 mg per package, preferably in a child-proof container.

Because of the conflicting recommendations on camphor-containing drug products, FDA has concluded that resolution of this issue would be in the public's best interest. Therefore, the agency has concluded that the Miscellaneous External Panel's recommendations should be available to the agency in developing a tentative final order on external analgesic drug products. By this notice, FDA announces that it is treating the data and information on camphor received from the Miscellaneous External Panel as a petition to reopen the administrative record on external analgesic drug products. FDA is granting the petition by allowing the data and information contained therein to be included in the administrative record for OTC external analgesic drug products. This notice serves to inform interested persons of these recommendations, which appear below. This reopening of the administrative record relates only to the ingredient camphor in OTC drug products. Comments relating to portions of the External Analgesic Proposed Monograph (44 FR 69768) other than on camphor will not be accepted at this time.

Statement of the Advisory Review Panel on OTC Miscellaneous External Drug Products Concerning OTC Drug Products Containing Camphor

The Advisory Review Panel on OTC Miscellaneous External Drug Products has reviewed the product camphorated oil as well as numerous other camphor-containing drug products submitted to it. On March 7, 1980, the Panel submitted its recommendation on Camphorated Oil and Camphor-Containing Drug Products for Over-the-Counter Human Use which requested that FDA remove camphorated oil from the market because it is unsafe due to the potential for poisonings resulting from accidental ingestion. The Panel understands that the agency is taking the necessary steps to implement its recommendation on camphorated oil and that this product will soon be eliminated from the OTC marketplace.

Camphor-Containing Products

In reviewing the many camphor-containing drug products submitted for external use, the Panel found little scientific evidence for the therapeutic use of camphor. The Panel is aware that some manufacturers have recently undertaken studies to show that camphor may have a counterirritant and antipruritic effect, but these studies are preliminary, and additional work is needed to determine what, if any, therapeutic benefit can be responsibly attributed to camphor.

Accordingly, because camphor appears to have little, if any, therapeutic benefit, the Panel has reviewed the safety of camphor and has come to some conclusions in evaluating the camphor benefit-to-risk ratio.

The Panel's evaluation of camphor as an ingredient in OTC drug products for external use has led to the conclusion that camphor should be classified as Category II for safety in concentrations of 2.5 percent or greater for any therapeutic use, including antimicrobial, antiseptic, analgesic, anesthetic, antipruritic, counterirritant, rubefacient, or "healing" action. The Panel concluded that products containing less than 2.5 percent camphor may be placed in Category I for safety, provided the package contains less than a total of 360 milligrams (my) camphor.

Numerous cases of accidental ingestion of products containing camphor have been reported. The Panel reported many of these cases in its recommendations on Camphorated Oil and Camphor-Containing Drug Products for Over-the-Counter Human Use (Ref. 1). In addition, the Panel would like to point out the following cases: A 2-year-old girl ingested approximately one to two teaspoonfuls of a liquid combination of 10.8 percent camphor and 4.7 percent phenol. She showed symptoms of anxiety, and her breath had a camphor odor. She recovered (Ref. 2). A 2-year-old boy swallowed approximately ½ ounce of camphor spirit containing 10 percent camphor, showed symptoms of burning in the mouth and throat and difficulty in breathing. He recovered after hospitalization (Ref. 3). A 77-year-old man swallowed 2 ounces of camphorated oil, had several grand mal

seizures and recovered after hemodialysis treatment (Ref. 4). A 37-year-old man ingested approximately 3 ounces of camphorated oil, exhibited symptoms of vomiting and grand mal seizures, was treated by resin hemoperfusion and lipid hemodialysis, and released the following day (Ref. 5).

The Panel's conclusion that camphor-containing drug products are unsafe is supported by recognized experts in the area of camphor poisoning. These experts include the following:

1. Carol Angle, M.D. (Ref. 6), past president of the National Clearinghouse for Poison Control Centers, who recommended that any OTC medicine containing camphor be limited to a maximum concentration of less than 2.5 percent to reduce the risk of accidental poisoning.

2. Harry Morton, Sc. D. (Ref. 7), a member of this Panel, who states that if a toxic dose of camphor is 30 mg/kg, a normal 2-year-old weighing 12 kg could suffer a toxic reaction with 360 mg camphor. The estimated minimum lethal dose of camphor in humans is 2 g for a 150 lb. man (30 mg/kg) when ingested orally (Ref. 1).

3. The American Academy of Pediatrics Committee on Drugs (Ref. 8) which concluded that:

a. Camphor has potent, and serious toxicologic actions, the ingestion of relatively small amounts having proven fatal.

b. Although accidental oral ingestion is the most common route of intoxication, significant quantities can be absorbed percutaneously and via inhalation.

c. Transplacental transfer may be toxic to the fetus.

In its recommendations on Camphorated Oil and Camphor-Containing Drug Products for OTC Human Use (Ref. 1) this Panel pointed out that camphor is readily absorbed through mucous membranes, subcutaneous tissue, and the gastrointestinal tract. In small doses, camphor combines with glucuronic acid and is excreted via the kidneys. This mechanism accounts for its unusually high toxicity in fetuses and in newborn infants because neither has developed the process of glucuronidation and, therefore, cannot detoxify camphor. The Panel also described a progressive symptomatology of severe camphor intoxication.

Camphor poisoning continues to be a national problem. Statistics compiled by the National Clearinghouse for Poison Control Centers (Ref. 9) for the years 1971 through 1978 show a total of 4,956 incidents involving camphor-related products. Of these, 4,541 were cases of accidental ingestion with 1,185 toxic reactions and 552 hospitalizations. Additionally, 3,878 of the 4,956 incidents occurred in children under 5 years of age; but, age was unspecified in 412 of the 4,956 incidents. Nor is there any indication of abatement of the camphor-accidental ingestion problem. On the contrary, there has been an increase in the number of incidents with camphor-related products in recent years, e.g., 805 in 1977 and 855 in 1978.

Camphor Spirit

Statistics compiled by the National Clearinghouse for Poison Control Centers record 211 incidents from 1971 through 1978 with camphor spirit, 190 of which were accidental ingestions with 160 occurring in children less than 5 years of age (Ref. 11). Camphor spirit is a product which consists of a 9 to 11 percent solution of camphor in alcohol (w/v). This product is currently official in the United States Pharmacopeia and National Formulary (Ref. 10). Camphor spirit was discussed specifically, although it was not submitted to any OTC drug review panel for evaluation, because this Panel believes that when camphorated oil disappears from the market, camphor spirit may become a substitute for it. This Panel also believes that camphor spirit should be placed in Category II for safety because the dangers from its accidental ingestion far outweigh its doubtful usefulness.

Summary

Based on the Panel's conclusion that camphor in concentrations of 2.5 percent and above has a low benefit-to-risk ratio, the Panel recommends that camphor be limited in OTC drug products for external use to less than 2.5 percent and that the quantity of camphor in a package be limited to a total of 360 mg per package which preferably will be closed with a child resistant lid.

References

(1) Advisory review Review Panel on OTC Miscellaneous External Drug Products, "Camphorated Oil and Camphor-Containing Drug Products for Over-the-Counter Human Use," published elsewhere in this issue of the **Federal Register.**

(2) Phelan, W. J., III, "Camphor Poisoning: Over-the-Counter Dangers," *Pediatrics,* 57:428–430, 1976.

(3) Jacobzine, H., and H. W. Raybin, "Briefs of Accidental Chemical Poisonings in New York City," *New York State Journal of Medicine,* 59:115–118, 1959.

(4) Ginn, H. E., et al., "Camphor Intoxication Treated by Lipid Dialysis," *The Journal of the American Medical Association,* 203:164–165, 1968.

(5) Kopelman, R., et al., "Camphor Intoxication Treated by Resin Hemoperfusion," *The Journal of the American Medical Association,* 241:727–728, 1979.

(6) OTC Volume 160222.

(7) OTC Volume 160358.

(8) Segal, S., et al., "Camphor: Who Needs It?," *Pediatrics,* 62:404–406, 1978.

(9) Poison Control Case Report Summary, National Clearinghouse for "Poison Control Centers," Food and Drug Administration, 1980.

(10) "The United States Pharmacopeia," 20th Revision, United States Pharmacopeial Convention, Inc., Rockville, MD, p. 113, 1980.

The OTC Volumes cited above are on public display in the Hearing Clerk's Office (HFA–305), Food and Drug Administration (address above).

Interested persons are invited to submit their comments in writing (preferably in four copies and identified with the Hearing Clerk docket number found in brackets in the heading of the document) regarding this notice on or before November 25, 1980. Comments should be addressed to the Hearing Clerk (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, and may be accompanied by a supporting memorandum or brief. Comments replying to comments may also be submitted on or before December 26, 1980. Comments may be seen in the above office between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 24, 1980.

William F. Randolph,

Acting Associate Commissioner for Regulatory Affairs.

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DEPARTMENT OF THE TREASURY

Internal Revenue Service

26 CFR Part 31

[LR–85–79]

Interest-Free Adjustment With Respect to Erroneous Filing of FICA and RRTA Returns

AGENCY: Internal Revenue Service, Treasury.

ACTION: Notice of proposed rulemaking.

SUMMARY: This document contains a proposed amendment which would permit an interest-free adjustment in certain circumstances where an employer erroneously either files a Federal Insurance Contributions Act (FICA) tax return instead of a Railroad Retirement Tax Act (RRTA) return, or files a RRTA tax return instead of a FICA tax return.