DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 358

[Docket No. 82N-0054]

Boil Treatment Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) boil treatment drug products (drug products for the temporary relief of pain an discomfort of boils) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by (March 28, 1988). New data by January 26, 1989.

Comments on the new data by March 27, 1989. Written comments on the agency's economic impact determination by May 25, 1988.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of June 29, 1982 (47 FR 28306), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking that would classify OTC boil ointment drug products as not generally recognized as safe and effective and as being misbranded and would declare these products to be new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)). The notice was based upon the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by September 27, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by October 27, 1982.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information.

In response to the advance notice of proposed rulemaking, one manufacturer and one consumer submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

In order to conform to terminology used in the OTC drug review regualtions (21 CFR 330.10), the present document is designated as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Subpart E of Part 358 (21 CFR Part 358, Subpart E), FDA states for the first time its position on the establishment of a monograph for OTC boil treatment drug products. Final agency action on this matter will occur with the publication at a future date of a final rule for OTC boil treatment drug products.

This proposal constitutes FDA's tentative conclusions on OTC boil treatment drug products based on the comments received and the agency's independent evaluation of the Panel's report. Although the Panel limited its deliberations to boil ointments, the agency believes that this rulemaking appropriately should apply to any OTC drug product labeled for the treatment of boils. Accordingly, the agency is now using the term "boil treatment" throughout this rulemaking rather than "boil ointment."

The OTC procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking, the agency stated that if it proposed to adopt the Panel's recommendations it would propose that OTC boil ointment drug products be eliminated from the OTC market effective 6 months after the date of publication of a final rule in the **Federal Register.** However, in this document the agency is proposing a monograph that would establish conditions under which OTC boil treatment drug products would be generally recognized as safe and effective and not misbranded. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written, ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling

to be in effect before 12 months after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products will have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

In the event that no new data are submitted to the agency during the allotted 12-month new data period or if submitted data are not sufficient to establish "monograph conditions" for OTC boil treatment drug products, the final rule will declare these products to be new drugs under section 201(p) of the act for which applications approved under section 505 of the act (21 U.S.C. 355) and 21 CFR Part 314 are required for marketing. Such rule will also declare that in the absence of an approved application, these products would be misbranded under section 502 of the act (21 U.S.C. 352). The rule will then be incorporated into 21 CFR Part 310, Subpart E—Requirements for Specific New Drugs or Devices, instead of into an OTC drug monograph in Part 358.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

1. One comment questioned the rationale for the agency's denial of its petition dated July 21, 1982 (Ref. 1) for an extension of time for submitting comments on the advance notice of proposed rulemaking. The petition was filed so that the results of testing and supporting information could be submitted together with its comments. The comment stated that other petitions for extension of time to comment on other advance notices of proposed rulemakings have been granted and cited the rulemaking for OTC weight control drug products in which an extension of 60 days was granted (47 FR 17576; April 23, 1982). The comment also cited the granting of extensions of the comment periods in the rulemaking for OTC relief of oral discomfort drug products (60 days) and for OTC oral health care drug products (90 days). The comment contended that the Agency provided no reason for granting those petitions while denying its request. The comment regarded this as arbitrary treatment and objected to the unexplained denial which came almost 2 months after the petition was filed and less than 2 weeks before the comment period ended.

The agency acknowledges that extensions of the comment period have been granted in other OTC drug rulemakings. In the three instances cited by the comment, the request for extension of the comment period was for the purpose of providing additional time to evaluate existing data and not to await test results as the comment indicated was its reason for needing more time. In each instance, the agency provided reasons for granting the extension. (See the **Federal Register** of April 23, 1982 (47 FR 17576) and July 30, 1982 (47 FR 32952 and 32953).) Likewise, the agency provided the comment reasons why its petition was denied. The agency stated that it is more appropriate to consider reopening the administrative record for the inclusion of test data when the data are actually available for submission to the agency (Ref. 2). The agency also suggested that when the company is prepared to submit the new data and information, it could then petition the agency to reopen the administrative record.

Neither the comment nor the company has petitioned the agency to reopen the administrative record since it closed on September 27, 1982. The agency points out that under 21 CFR 330.10(a)(7), any comments on this tentative final monograph may be submitted within 60 days of the publication date in the **Federal Register**, and new data may be submitted within 12 months.

References

(1) Comment coded EXT, Docket No. 82N–0054, Dockets Management Branch.

(2) Letter to P.S. Reichertz from J.P. Hile, FDA, coded ANS, Docket No. 82N–0054, Dockets Management Branch.

2. One comment contended that the proposed regulation in the advance notice of proposed rulemaking is not based on any fact in the administrative record and is therefore arbitrary and capricious. The comment stated that the Panel's evaluation, which is the basis of the proposed rule, was limited to three short paragraphs at 47 FR 28308 and that there is nothing in the administrative record that supports the Panel's conclusion that OTC boil ointment drug products are not safe and effective. The comment stated that the Panel did not at any point in its evaluation cite or refer to an instance—a study, report, consumer complaint, or any other item of evidence—which would support its position. The comment concluded that the Panel's finding is conclusory and without any support whatsoever in the administrative record. The comment stated its belief that a rule based upon such an evaluation is arbitrary and capricious and would not withstand judicial scrutiny. The comment cited a number of court cases to support its position that a rule will not be sustained where there are inadequate facts in the record to support it, and thus the matter should be remanded to the agency for further consideration (Ref. 1).

The Panel evaluated boil ointment drug products over the course of seven meetings (47 FR 28307). In its evaluation, the Panel mentioned that it received three submissions for this type of product (47 FR 28308) and that there were eight labeled ingredients contained in the marketed products submitted (47 FR 28307). The Panel classified these 8 ingredients, plus 16 other active ingredients in boil treatment drug products, in Category II, not because of a disregard of the evidence in the administrative record, but because of its belief that the self-treatment of boils is not desirable because improper treatment or a delay in receiving proper professional treatment may cause the infection to spread. The agency has

considered the Panel's recommendations and has thoroughly evaluated all three submissions that were made to the Panel (Refs. 2, 3, and 4), as well as the comments received in response to the advance notice of proposed rulemaking and is tentatively concluding that there may be a need for such products. (See comment 5 and Part II below.) Based on that evaluation, the agency is proposing in this tentative final monograph to reclassify certain ingredients from Category II to Category III and is encouraging the submission of additional data and information to support the claims of safety and efficacy for currently marketed OTC boil treatment drug products. (See comment 5 and Part II below.) The comment's concerns that the final rule be supported by the facts in the administrative record will be addressed as the rulemaking proceeds through its subsequent steps.

References

(1) Comment No. C00001, Docket No. 82N-0054, Dockets Management Branch.
(2) OTC Volume 160005.
(3) OTC Volume160182.
(4) OTC Volume 160214.

3. One comment was against "putting more control of pharmaceutical disbursements in the hands of physicians than is necessary." The comment argued that physicians are "hard to get into see," are costly, and "do not want to be bothered until something is major." The comment contended that removal of boil ointment drug products from the OTC market would require that individuals see a doctor for relief. The comment recommended that the physician be taken out of prescribing "simple medication care" because it is time consuming, expensive, a misuse of physician resources, and a cause of unnecessary health care expense.

The purpose of the OTC drug review is to ensure that OTC drug products are safe and effective. Accordingly, the review will result in the removal of unsafe or ineffective drug products from the OTC market. Also, some products may be reformulated to contain ingredients that are found to be generally recognized as safe and effective. Products already on the market which contain ingredients that are generally recognized as safe and effective will remain available to consumers.

In some cases, entire classes of OTC products such as daytime sedatives and anticholinergics used in cough-cold drug products have been removed from the OTC market because the agency concluded that these products were not appropriate for OTC use. (See the **Federal Register** of June 22, 1979 (44 FR 36378) and November 8, 1985 (50 FR 46582).) However, in the case of boil treatment drug products, after reviewing the Panel's recommendations and the comments received, the agency questions the Panel's recommendations and believes that there may be a need for OTC boil treatment drug products. However, because no ingredients are in Category I at this time and because more data are needed, the agency is unable to determine until this rulemaking is completed whether boil treatment drug products will remain available OTC.

4. One comment, from the manufacturer of an OTC anesthetic and antiseptic ointment drug product marketed for the temporary relief of discomfort of boils, noted that if the agency accepts the Panel's Category II recommendation for all OTC boil treatment drug products, then its product would be eliminated from the OTC market (Ref. 1). The comment stated that marketing experience of its product has not indicated any safety problem associated with the OTC treatment of boils and this marketing experience shows that the product is safe for OTC use within the meaning of 21 CFR 330.10(a) (4) (i), which permits the use of marketing experience in the evaluation of the safety of an OTC drug product. The comment stated that its product has been marketed for over 27 years with over 1½ million units sold in the last 6 years and demand is increasing for the product. The comment also stated that only 18 complaints were received during the last 6 years—10 concerning mild irritation caused by the product and 8 claiming lack of effectiveness.

As discussed in comment 5 below, the agency believes that there may be a need for OTC boil treatment drug products. Even though the agency is upgrading several ingredients to Category III, there are no Category I ingredients at this time. (See Part II below.) Unless one or more of the Category III ingredients are upgraded to Category I in the final rule, the comment is correct in stating that OTC boil treatment drug products will be eliminated from the market.

The agency has considered the marketing experience of the product, which contains ichthammol, camphor, benzocaine, sulfur, phenol, and juniper tar, and evaluated the manufacturer's previous submission to the Panel (Ref. 2). (See Part II below.) The agency agrees with the comment that marketing experience can be used to support the safety of a product; nevertheless, the manufacturer did not provide sufficient information to support the safety and effectiveness of its product in the treatment of boils. As discussed in Part II below, the agency is classifying the ingredients listed above in Category III at this time and is inviting the submission of additional data and information to substantiate the safety and effectiveness of these ingredients for the treatment of boils.

References

(1) Comment Nos. C00001 and CR, Dockets Management Branch, Docket No. 82N-0054.
(2) OTC Volume 160005.

5. One comment (Ref. 1) disagreed with the Panel's conclusion that self-treatment of boils is not in the best interest of the consumer because improper treatment or a delay in receiving proper professional treatment for boils may cause the infection to spread. The comment stated that there is no safety problem associated with the treatment of boils with OTC drugs based upon marketing experience, scientific evidence, and the conclusions of leading experts in the field of dermatology and infectious diseases. The comment contended that the Panel had not cited any incidence of systemic infection which resulted from the temporary use of OTC boil ointment products. The comment added that it has received no complaints that use of its product, which has been marketed for over 27 years, has resulted in a delay in treatment that caused an infection to spread. The comment claimed that the Panel's conclusion was based on a hypothetical safety concern for which it could provide no reference and that the scientific evidence shows that human skin is difficult to infect experimentally with virulent staphylococci and/or streptococci and that, once infected, it is equally difficult to maintain the infection without seriously altering or compromising the skin of the host (Refs. 2 through 6).

The comment contended that the Panel ignored evidence (Ref. 7) that showed there is a need for a product directly available to consumers which is properly formulated to provide temporary relief from pain of boils which at the same time prevents further infection. The comment submitted a survey (Ref. 8) and contended that more than 83 percent of patients with boils suffer pain along with a boil. The comment added that relief of pain will prevent a consumer from attempting to manipulate or needle a boil and thus prevents further topical spread of infection.

The comment provided affidavits containing the views of experts in the

field of dermatology and infectious diseases regarding the safe and effective use of OTC boil ointments (Refs. 9, 10, and 11). The comment stated that the experts believe that most persons with boils never seek medical attention and that they do not require the sophisticated and expensive services of a physician because the vast majority of boils are well managed by normal host defenses and are thus self-limited. The experts referred to and agreed with the Panel's statement on boils at 47 FR 28308 that "these infections are usually minor." The comment added that the experts recognize that it can be argued that neglect of boils may lead to a need for surgery or systemic antibiotics that might not otherwise have been required; however, it cannot be argued convincingly that topical boil preparations are more likely to lead to this eventuality than hot compresses or other home remedies.

The agency agrees that the marketing experience described by the comment is supportive of the safety and effectiveness of OTC boil treatment drug products, but this experience cannot be used as the sole criterion for determining that these products are safe and effective for OTC use. After reviewing the Panel's recommendations, the data and information submitted by the comment, and the affidavits of experts in the field of dermatology and infectious diseases, the agency is tentatively concluding that there may be a need for OTC boil treatment drug products.

The agency finds that the references cited by the comment (Refs. 2 through 6) show that human skin is remarkably resistant to staphylococcal and streptococcal infection.

Duncan, McBride, and Knox (Ref. 2) state that streptococci could rarely be recovered from the skin 24 hours after removing an occlusion of the skin of children with clinical impetigo. In another experiment, *Staphylococcus pyogenes* (*S. pyogenes*) disappeared completely from the skin within 5 hours in 50 percent of their adult subjects. The authors pointed out that occlusion has been requisite in all methods of inducing infection whether the organism is yeast, dermatophyte, or bacteria, and that occlusion to the degree required for successful experimental infection rarely, if ever, occurs naturally so that the conditions of natural infection have yet to be defined.

In another study, Duncan, McBride, and Knox (Ref. 3) describe a technique of applying staphylococcus and streptococcus in the form of an overnight broth culture, stabbing through the drop of inoculum with a blood lancet, and covering the site with nonporous plastic tape. Four areas on each subject were inoculated in an identical manner. This experiment was conducted to find a reproducible experimental skin infection so that further studies could be undertaken on the pathogenesis of cutaneous infections. Successful infection of the back in 15 percent, the arm in 13 percent, the thigh in 21 percent, and the leg in 38 percent of the attempts provided further evidence that skin is difficult to infect.

Foster and Hutt (Ref. 4) introduced staphylococci into artificial skin lesions to try to determine whether local conditions influenced multiplication of organisms or the course of the subsequent lesion, whether different types of staphylococci varied in pathogenicity, and what was the smallest infecting dose. Covered lesions showed a considerable increase in the numbers of organisms between 2 and 8 hours, followed by a slower increase over the next 14 hours; whereas, there was virtually no increase in numbers in the uncovered lesions even after 24 hours.

Singh, Marples, and Kligman (Ref. 5) reported that *Staphylococcus aureus* (*S. aureus*) infections have been consistently induced in normal human skin by applying large inocula to areas degermed with ethanol and kept moist under occlusive dressing. The organisms were confined to the surface and did not proliferate within the living portion of the skin. Removal of the dressing was followed by swift death of almost all organisms, followed by immediate resolution of the lesion within a few days.

Elek (Ref. 6) discusses a number of experiments on man that were conducted to establish whether or not differences in the resulting lesions could be demonstrated (by pus formation) between randomly selected nasal strains of *S. pyogenes* and other strains obtained from human lesions, which were therefore presumed to be virulent. Elek concluded that man appears to possess a high degree of natural resistance to *S. pyogenes*. No differences in the virulence of known pyogenic strains and nasal strains from unselected carriers could be demonstrated by accepting pus formation in man as the criterion of virulence.

Although the studies above show the difficulty in producing skin infection, none of the references specifically discusses the relationship of staphylococcal and streptococcal infection to the occurrence of boils. However, Bynoe (Ref. 12) comments on Elek's suggestion (Ref. 6) that there is no difference in the virulence of different strains of coagulase-positive staphylococci, whether from pyogenic lesions or from nasal carriers. Bynoe referred to a specific case in which a nurse came on duty with a boil on her face, and, within a few days, there were two severe infections in the nursery. Cultures from the nurse with the boil and from the two infected babies were all the same type.

The specific case cited by Bynoe (Ref. 12) would support the possibility that infection from boils can occur. However, in light of the other studies (Refs. 2 through 6) that support the difficulty of producing skin infection, the agency believes that a safety concern that infection may spread may not be a major problem. However, the agency concludes that additional information is needed before the agency can fully address the Panel's concerns that improper treatment or a delay in receiving professional treatment for boils may cause the infection to spread.

The results of the survey submitted by the comment (Ref. 8) can be summarized as follows: The rate of furunculosis (occurrence of boils) remains low in the United States with regional variations from 1.4 to 3.0 percent; persons plagued with boils average 2.89 attacks per year with males being more susceptible than females; symptoms that disturbed boil sufferers most were primarily pain (219 out of 257) and secondly cosmetic appearance (32 out of 257); approximately 72 percent of boil sufferers did not visit a physician; patients with boils visited a physician more frequently as the number of boils increased, indicating that patients know when to contact a physician; in self-medication approximately 49 percent of sufferers used medication, 45 percent used compresses, and 12 percent did nothing at all; and the majority of sufferers were satisfied with the treatment used while only 11 percent felt the treatment was not satisfactory. In addition, the survey indicated that 175 subjects were satisfied with their treatment as opposed to 28 subjects who were dissatisfied. For drugs being evaluated in the OTC drug review, the number of very satisfactory and somewhat satisfactory treatment evaluations compared to the number of not very satisfactory and not at all satisfactory treatment evaluations was 16 to 2 for the comment's product, 6 to 0 for a product containing ichthammol, and 8 to 0 for an unspecified drawing salve. The survey also indicated that patients visited a physician more frequently as the number of boils

increased, suggesting that patients are alerted to contact a physician if the condition is more than something minor or if the treatment is ineffective.

In one of the affidavits submitted by the comment, Ulrich (Ref. 9) concluded that the data above are convincing proof of the need for OTC boil ointment drug products. Ulrich stated that boils last from several days to several weeks and are generally defined as an infection of the hair follicle which produces a painful cellulitis with *S. aureus* as the most common infecting organism, but other pyogenic cocci and bacilli or gram negative bacteria may also be involved.

In another affidavit, Duncan (Ref. 10) stated that over a 15-year practice many patients "present with their second or third inflammatory episode with a boil—the initial episode(s) having resolved to the patients' satisfaction, with or without OTC medicament, demonstrating the basic tendency of boils not to spread." Duncan also discussed the studies (Refs. 2 through 6) described above and concluded that human skin is difficult to experimentally infect with virulent staphylococci and/or streptococci and that the spread of infection from a boil is remote.

In the third affidavit, Drutz (Ref. 11) stated that most persons with boils never seek medical attention and that most patients do not require the sophisticated and expensive services of a physician because the vast majority of boils are well managed by normal host defenses and are thus self-limited. Drutz also states that local spread of boils may occur from one locus to another, or spread may be hematogenous with septicemia, metastatic abscess formation, or even endocarditis. However, Drutz contends that evidence that topical preparations increase the risk of spread in patients with chronic recurring boils is lacking.

Based on the information provided in the affidavits, the results of the survey, and the references to support the suggestion that the spread of infection may not be a serious problem, the agency tentatively concludes that there may be a need for OTC boil treatment drug products. Although there appears to be minimal safety problems in the self-treatment of boils, the agency believes that these products should be used only for a limited amount of time and that if the boil worsens, then the labeling of the product should direct the consumer to see a doctor. Accordingly, the agency is proposing that these products contain warning information not to use the product for more than 7 days and if the condition worsens, to consult a doctor. The warning is based on the results listed in Table 6 of the survey (Ref. 8) in which the number of sufferers who had a doctor treat a boil is compared to the number of days the sufferer had the boil before seeing the doctor. The comparison includes groups of sufferers from various geographic areas as well as groups segmented by sex and age. The average number of days before sufferers saw a doctor was 6.32. The agency is therefore proposing 7 days to be consistent with a number of other OTC drug rulemakings which provide for a 7-day limitation for use. (See, for example, the tentative final monograph for OTC external analgesic drug products (48 FR 5852; February 8, 1983) and the tentative final monograph for OTC skin protectant drug products (48 FR 6820; February 15, 1983).)

Based upon the results of this survey and the additional references, the agency has upgraded some of the ingredients used in OTC boil treatment drug products from Category II to Category III. The agency is interested in receiving additional public comment on the usefulness of these products and on whether self-treatment of boils is appropriate. The agency is also requesting additional clinical data from studies conducted in the target population demonstrating that the ingredients used in OTC boil treatment drug products are safe and effective for this use.

References

(1) Comment Nos. C00001, CR, CR0002, CR0003, and SUP, Docket No. 82N–0054, Dockets Management Branch.

(2) Duncan, W.C., M.E. McBride, and J.M. Knox, "Experimentally Induced Cutaneous Infections in Man," *in* "Skin Microbiology. Relevance to Clinical Infection," Edited by H.I. Maibach and R. Aly, Springer-Verlag, New York, pp. 220–230, 1981.

(3) Duncan, W.C., M.E. McBride, and J.M. Knox, "Experimental Production of Infection in Humans," *Journal of Investigative Dermatology*, 54:319–323, 1970.

(4) Foster, W.D., and M.S.R. Hutt, "Experimental Staphylococcal Infections in Man," *Lancet*, 2:1373–1375, 1960.

(5) Singh, G., R.R. Marples, and A.M. Kligman, "Experimental *Staphylococcus Aureus* Infections in Humans," *Journal of Investigative Dermatology*, 57:149–162, 1971.

(6) Elek, S.D., "Experimental Staphylococcal Infections in the Skin of Man," *Annals of the New York Academy of Sciences*, 65:85–89, 1956.

(7) OTC Volume 160005.

(8) Home Testing Institute, "Boil-Ease Study No. 7034," Unpublished study in Comment No. SUP, Docket No. 82N–0054, Dockets Management Branch.

(9) Ulrich, J.A. Affidavit contained in Comment No. SUP, Docket No. 82N–0054, Dockets Management Branch.

(10) Duncan, W.C., Affidavit contained in Comment No. SUP, Docket No. 82N–0054, Dockets Management Branch.

(11) Drutz, D.J., Affidavit contained in Comment No. SUP, Docket No. 82N–0054, Dockets Management Branch.

(12) Bynoe, E.T., Discussion of the Paper, "Experimental Staphylococcal Infections in the Skin of Man," *Annals of the New York Academy of Sciences*, 65:89–90, 1956.

II. The Agency's Evaluation of the Submissions

Because the Panel did not review specific ingredients or products for use in OTC boil ointment drug products, the agency has reviewed all the submissions to the Panel and has the following specific comments:

1. One submission to the Panel contained information on a marketed product containing 40 to 43 percent magnesium sulfate labeled as a drawing ointment for external application to pimples and blemishes associated with acne and also for boils and carbuncles (Ref. 1).

The submission did not contain any clinical data or information on the use of magnesium sulfate for the relief of boils, but did contain a very brief overview of the historical use of magnesium sulfate and a discussion regarding osmotic pressure and the resulting drawing action of magnesium sulfate. A brief summary of the submission follows.

Magnesium sulfate (epsom salts) has been used for many years to alleviate local inflammatory conditions by using concentrations of 20 to 50 percent in warm water to reduce common inflammation by virtue of an osmotic gradient action. Magnesium sulfate provides a drawing action using the mechanism of osmotic pressure which brings about diffusion between solutions of different concentrations or between a solute and the fluid in which it is dissolved. A concentration of the magnesium ion on the skin surface causes fluid of the skin tissue to move the skin surface. The greatest concentrations of magnesium sulfate needed to bring about osmotic pressure sufficient to withdraw tissue fluids would be absorbed by the skin in only a small amount, and the body would tolerate even larger quantities without side effects. The submission pointed out that the marketed product is a saturated solution of magnesium sulfate incorporated into a hydrophilic ointment base, and that the effectiveness of the product as a drawing ointment for boils and carbuncles is due to the fact that there is twice as much saturated solution of magnesium sulfate as there is ointment base and, as a result, the product works by the principle of osmotic pressure. The submission added that magnesium sulfate in a wet dressing or hot pack relieves pain by its

local anesthetic effect and relieves swelling by withdrawing fluid from the tissues.

Regarding safety, the submission stated that magnesium sulfate can be taken internally as a saline cathartic in doses of 15 grams (g) and is not absorbed from the intestinal tract. (FDA supported the safety of taking large doses of magnesium sulfate internally when the agency issued a tentative final monograph for OTC laxative drug products in the **Federal Register** of January 15, 1985 (50 FR 2124) and proposed Category I status for magnesium sulfate in doses of 10 to 30 g as a saline laxative.) The submission contended that very little, if any, magnesium sulfate is absorbed from its ointment product because, in the principle of osmotic pressure, the fluid comes toward the surface of the skin or the area at the greatest concentration of the magnesium ion, with very little magnesium sulfate being absorbed.

Another submission to the Panel contained a label for a product containing magnesium sulfate 18.3 g (61 percent) and benzocaine 150 milligrams (mg) (0.5 percent) in each 30 g of propylene glycol base (Ref. 2). The label stated that the product was a local anti-inflammatory agent to be used as a topical dressing for minor infections such as boils and pimples. The submission did not contain any additional information.

These two submissions did not contain sufficient information to support the effectiveness of magnesium sulfate and benzocaine for the labeled claims. However, the agency concludes that 40 to 61 percent magnesium sulfate is safe when used externally. Based on the information submitted, the agency cannot determine whether magnesium sulfate is effective in treating boils and is classifying this ingredient in Category III at this time. The use of benzocaine is discussed below. (See paragraph 2(c) below.)

References

(1) OTC Volume 160214.

(2) OTC Volume 160182.

2. The third submission (Ref. 1) to the Panel contained information on a product claiming to be a pain-relieving drawing salve for boils and an anesthetic-antiseptic. Because the submission was dated January 10, 1974, the agency obtained a package of the currently marketed product; it listed the active ingredients as ichthammol 1.86 percent, camphor 1.6 percent, benzocaine 0.5 percent, sulfur 0.44 percent, phenol 0.42 percent, and juniper tar 0.11 percent and was labeled as an antiseptic drawing salve and for fast relief from painful boils. The list of ingredients in the submission and in the currently marketed product differ (rosin and thymol have been deleted and sulfur has been added); accordingly, the agency is discussing and classifying only the ingredients in the currently marketed product.

[**Note.**— The agency recently became aware that the product has been reformulated again and has also been relabeled (Ref. 2). Nevertheless, none of the agency's tentative conclusions discussed in this document are affected by these changes because the administrative record lacks sufficient information regarding the use of the product's ingredients for the treatment of boils. The agency invites the submission of additional information.]

(a) *Ichthammol.* This ingredient has been used for the treatment of boils (Refs. 3 and 4) and has been used for a variety of skin disorders because of its anti-inflammatory, vasoconstrictive, astringent, irritant, antibacterial, emollient, demulcent, and antiseptic properties (Refs. 3 through 7). It has also been reported to cause hyperepithelialization (Ref. 4) and to produce a local stimulant effect which tends to improve peripheral circulation (Ref. 7). Although historically ichthammol has been commonly referred to as a "drawing" salve for the treatment of boils, the submission did not include any clinical data that demonstrate such an effect. Because of insufficient information at this time, the agency cannot determine whether this ingredient is safe and effective in a concentration of 1.86 percent as an antiseptic or for its "drawing" action for the treatment of boils. Therefore, the agency is classifying ichthammol in Category III.

(b) *Camphor.* Camphor has been classified as a Category I analgesic, anesthetic, and antipruritic in the tentative final monograph for OTC external analgesic drug products. (See the **Federal Register** of February 8, 1983; 48 FR 5867 to 5868.) In that publication, the agency concurred with the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products that camphor in concentrations of 0.1 to 3 percent is safe and effective for the temporary relief of pain, itching, or pain and itching associated with monor burns, sunburn, minor cuts, scrapes, insect bites, or minor skin irritations. Because the tentative final monograph for OTC external analgesic drug products does not specifically discuss the use of camphor for the treatment of boils and because the submission to this rulemaking contained insufficient information, the agency is classifying camphor in a concentration of 1.6 percent in Category III.

(c) *Benzocaine.* While the submission to this rulemaking (Ref. 1) contained published articles regarding the safety and effectiveness of benzocaine, none involved the use of benzocaine on boils Benzocaine was also classified in Category I in the external analgesic tentative final monograph for the temporary relief of pain, itching, or pain and itching in concentrations of 5 to 20 percent. Because the submission contained insufficient information that benzocaine in a concentration of 0.5 percent is safe and effective for the treatment of boils, the agency is classifying this ingredient in Category III.

(d) *Sulfur.* The only discussion of sulfur in the submitted information was a brief reference to its use in the treatment of scabies in a naval hospital (Ref. 8); there is no mention of its use in the treatment of boils. The agency assumes the intended use of sulfur in the product relates to the antiseptic claim in the products' labeling. In this light, the agency notes that in the advance notice of proposed rulemaking for OTC antifungal drug products that was published in the **Federal Register** of March 23, 1982 (47 FR 12480), sulfur was described as an antifungal agent due to its keratolytic effect and was classified in Category III. (See 47 FR 12549.) Similarly, in the same issue of the **Federal Register** (47 FR 12430), the advance notice of proposed rulemaking for OTC acne drug products discusses the rationale for the use of sulfur in acne because of its keratolytic and antibacterial effects. (See 47 FR 12447.) Sulfur was classified in Category I in that rulemaking. However, because there is insufficient information for the use of sulfur in a concentration of 0.44 percent to treat boils, the agency is placing this ingredient in Category III at this time.

(e) *Phenol.* In the **Federal Register** of January 6, 1978 (43 FR 1210), the Advisory Review Panel for OTC Antimicrobial Drug Products classified phenol in Category III for several antimicrobial uses in concentrations of 1.5 percent or less. In the **Federal Register** of February 8, 1983 (48 FR 5852), phenol 0.5 to 1.5 percent was classified in Category I as an analgesic, anesthetic, and antipruritic. (See 48 FR 5867.) Because these rulemakings do not address the use of phenol in the treatment of boils and because there is insufficient information to make a determination at this time, the agency is classifying phenol in Category III.

(f) *Juniper tar.* In the tentative final monograph for OTC external analgesic drug products, juniper tar in concentrations of 1 to 5 percent was classified in Category I as an analgesic, anesthetic, and antipruritic (48 FR 5867). However, because that rulemaking did not specifically address the use of juniper tar for the treatment of boils and because there is insufficient information in the submission to this rulemaking, the agency cannot make a determination on the safety and effectiveness of juniper tar in a concentration of 0.11 percent at this time. Therefore, the agency is classifying juniper tar in Category III at this time.

The submission did not contain any safety or effectiveness data on the use of any of the ingredients above individually in treating boils. Clinical data are needed to establish the safety and effectiveness of using these ingredients to provide relief from the pain and discomfort of boils. The "drawing" action of ingredients such as magnesium sulfate or ichthammol and the antiseptic action of sulfur and phenol on a boil needs to be shown clinically. Without such information, the agency is unable to determine that any of these ingredients are generally recognized as safe and effective for these uses.

References

(1) OTC Volume 160005.

(2) Letter from H.W. Gordon, Commerce Drug Co., Inc., to W.E. Gilbertson, FDA, is contained in OTC Volume 16LTFM.

(3) Wilkinson, D.S., "Topical Therapy," *in* "Textbook of Dermatology," 2d Ed., Volume II, edited by A. Rook, D.S. Wilkinson, and F.J.G. Ebling, Blackwell Scientific Publications, Oxford, p. 2072, 1972.

(4) Harvey, S.C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 17th Ed., edited by A.R. Gennaro, Mack Publishing Co., Easton, PA, p. 781, 1985.

(5) Reynolds, J.E.F., and A.B. Prasad, editors, "Martindale. The Extra Pharmacopeia," 28th Ed., The Pharmaceutical Press, London, p. 496, 1982.

(6) Harvey, S.C., "Antiseptics and Disinfectants," *in* "Goodman and Gilman's The Pharmacological Basis of Therapeutics," 7th edition, edited by L.S. Goodman and A. Gilman, Macmillan Publishing Co., New York, p. 972, 1985.

(7) Osol, A. and R. Pratt, The United States Dispensatory, 27th edition, J.B. Lippincott Co., Philadelphia, p. 610, 1973.

(8) Carpenter, C.C., et al., "Scabies and Pediculosis Treated with Benzyl Benzoate, DDT, Benzocaine Emulsion," *The Journal of Investigative Dermatology,* 14:93–98, 1946.

III. The Agency's Tentative Conclusions on OTC Boil Treatment Drug Products

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions

1. Summary of Ingredient Categories

The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has made some changes in the categorization of boil treatment active ingredients recommended by the Panel. As a convenience to the reader, the following list is included as a summary of the categorization of boil treatment active ingredients recommended by the Panel and the proposed categorization by the agency.

Boil ointment active ingredients	Panel	Agency
Aminoacridine hydrochloride	II	II
Benzocaine	II	III
Bismuth subnitrate	II	II
Camphor	II	III
Cholesterol	II	II
Extract of ergot	II	II
Hexachlorophene	II	II
Ichthammol	II	III
Isobutamben[1]	II	II
Juniper tar (oil of cade)	II	III
Lanolin	II	II
Magnesium sulfate	II	III
Menthol	II	II
Mercurous chloride	II	II
Methyl salicylate	II	II
Oil of sassafras	II	II
Oxyquinoline sulfate	II	II
Petrolatum	II	II
Phenol	II	III
Pine tar	II	II
Rosin	II	II
Rosin cerate	II	II
Sulfur	NA	III
Thymol	II	II
Zinc oxide	II	II

[1] Although "isobutyl-p-aminobenzoate" was the name designated by the Panel for this ingredient, "isobutamben" is the official title for this ingredient in the "USAN and the USP dictionary of drug names, 1987."

2. Testing of Category II and Category III Conditions

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any boil treatment ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. Based on submitted information not available to the Panel, the agency tentatively concludes that there may be a need for OTC boil treatment drug products and that manufacturers should be afforded an opportunity to provide additional data to support continued marketing of these drug products. In addition, the agency is proposing the following warning, "Do not use this product for more than 7 days. If condition worsens or does not improve, consult a doctor." (See Part I. paragraph 5. above.) The agency is also proposing two additional warnings, "For external use only" and "Avoid contact with the eyes." Use of both statements is consistent with the warnings included in a number of other OTC drug monographs for topical drug products. (See, example, the tentative final monograph for OTC external analgesic drug products (48 FR 5852; February 8, 1983); the tentative final monograph for OTC skin protection drug products (48 FR 6820; February 15, 1983); and the final monograph for OTC topical otic drug products (51 FR 28656; August 8, 1986).)

2. The agency is aware that a manufacturer of an OTC boil treatment drug product filed comments following the publication of the tentative final monograph for OTC external analgesic drug products (Ref. 1). The manufacturer raised two basic issues involving labeling of boil treatment products. One issue was a request to revise the labeling indication for local anesthetics used as external analgesics to include relief of pain and itching associated with boils. This request will be considered within the context of the external analgesic rulemaking at a later date. The other issue, which concerned an additional warning for boil treatment drug products, will be addressed in this document. The manufacturer suggested the additional warning as follows: "Do not use on boils on the lips, nose, cheeks, or forehead. Seek professional assistance for treatment of boils in these areas." The manufacturer also stated that an additional warning statement is needed to warn consumers to consult a doctor "if fever or redness around the boil develops."

The agency notes that the Panel stated that the use of systemic antimicrobial therapy is indicated for boils associated with a surrounding redness or those associated with fever, or located on the upper lip, nose, cheeks, or forehead. (See 47 FR 28308). After reviewing the Panel's comments, the agency agrees with the manufacturer that the additional warnings are needed. Accordingly, the agency is including the warning recommended by the manufacturer but is making a minor revision to make the wording more consistent with other tentative final monographs. The agency is revising the limitation for use warning discussed in paragraph 1 above to include the manufacturer's suggested warning statement regarding the development of fever or redness around a boil but is revising the statement for clarity. The revised warnings will read, "Do not use on boils on the lips, nose, cheeks, or forehead: Consult a doctor for treatment of boils in these areas" and "Do not use this product for more than 7 days. If condition worsens or does not improve, if fever occurs, or if redness around the boil develops, consult a doctor."

Reference

(1) Comment No. C00081, Docket No. 78N-0301, Dockets Management Branch.

3. The agency is proposing that magnesium sulfate, benzocaine, camphor, ichthammol, juniper tar, and phenol be reclassified from Category II to Category III and that sulfur be classified in Category III. (See Part II. paragraphs 1. and 2. above.)

In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing its labeling policy for stating the indications for use of OTC drug products. Under the final rule, the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph where exact language has been established and identified by quotation marks in an applicable monograph or other regulation, e.g., 21 CFR 201.63 or 330.1(g). The proposed rule in this document is subject to the final rule revising the labeling policy.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC boil ointment drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Pub. L. 96-354. That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC boil ointment drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC boil ointment drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by May 25, 1988. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before March 28, 1988, submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before May 25, 1988. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

Interested persons, on or before January 26, 1989, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before March 27, 1989. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on March 27, 1989. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 358

Labeling, Over-the-counter drugs, Boil treatment drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 358 (proposed in the **Federal Register** of September 3, 1982; 47 FR 39108), by adding new Subpart E, to read as follows:

PART 358—MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart E—Boil Treatment Drug Products

Sec.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); 5 U.S.C. 553; 21 CFR 5.10 and 5.11.

Subpart E—Boil Treatment Drug Products

§ 358.401 Scope.

(a) An over-the-counter boil treatment drug product in a form suitable for topical application is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart and each of the general conditions established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 358.403 Definition.

As used in this subpart:

Boil treatment drug product. A drug product for the temporary relief of pain and discomfort of boils.

§ 358.410 Boil treatment active ingredients. [Reserved]

§ 358.450 Labeling of boil treatment drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "boil treatment."

(b) *Indications.* The labeling of the product states under the heading "Indications," the following: "For the temporary relief of pain and discomfort of boils." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph (b), may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of the act relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) "Do not use on boils on the lips, nose, cheeks, or forehead. Consult a doctor for treatment of boils in these areas."

(2) "For external use only."

(3) "Avoid contact with the eyes."

(4) "Do not use this product for more than 7 days. If condition worsens or does not improve, if fever occurs, or if redness around the boil develops, consult a doctor."

(d) *Directions.* [Reserved]

Dated: October 30, 1987.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 88–1454 Filed 1–25–88; 8:45 am]

BILLING CODE 4160–01–M