DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 82N-0054]

RIN 0905-AA06

Boil Treatment Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that over-the-counter (OTC) boil treatment drug products are not generally recognized as safe and effective and are misbranded. This final rule applies only to topical drug products used to reduce the size of a boil or to reduce an infection related to a boil. Certain drug products used to provide relief of local symptoms (itch, pain, and discomfort) of a boil will be addressed in the rulemaking for OTC external analgesic drug products in a future issue of the Federal Register. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on OTC boil treatment drug products that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: May 16, 1994.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-594-5000.

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 (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, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC boil treatment drug products was published in the Federal Register of January 26, 1988 (53 FR 2198). Interested persons were invited to file by March 28, 1988, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by May 25, 1988. New data could have been submitted until January 26, 1989, and comments on the new data until March 27, 1989. Final agency action on that proposal occurs with publication of this final rule on OTC boil treatment drug products.

In the tentative final monograph, no active ingredients were proposed as generally recognized as safe and effective and not misbranded for the treatment of boils. However, the agency proposed labeling in § 358.450(b) in the event that data were submitted that resulted in the upgrading of any ingredients to monograph status in the final rule. The proposed indication was "For the temporary relief of pain and discomfort of boils."

The primary types of products used in the drug treatment of boils are: (1) Antibacterial "drawing salves" to reduce boil size and infection, and (2) anesthetics to relieve local symptoms, such as itch, pain, and discomfort. The agency stated in the tentative final monograph (53 FR 2198 at 2204) that clinical data were needed to demonstrate the "drawing action" on a boil of ingredients such as magnesium sulfate or ichthammol, and to demonstrate the antiseptic action of sulfur and phenol. The agency also stated that if new data that were submitted during the allotted 12-month comment and new data period were not sufficient to establish monograph conditions for OTC boil treatment drug products, the final rule would declare these products to be new drugs (53 FR 2199). In this final rule, the agency concludes that no active ingredient has been shown to be generally recognized as safe and effective for use as a drawing agent or antiseptic in OTC boil treatment drug products. The agency also concludes that several other ingredients are not generally recognized as safe and effective for use as a topical analgesic, anesthetic, and antipruritic in OTC boil treatment drug products. No substantive data were submitted for these ingredients.

As discussed, the labeling proposed in part 358 for OTC boil treatment drug products applied primarily to products used for the temporary relief of pain and discomfort of boils. Among the ingredients considered for this indication were several topical analgesic, anesthetic, and antipruritic active ingredients (benzocaine, camphor, juniper tar, menthol, and phenol) that are also being considered in the OTC external analgesic rulemaking. However, with the exception of benzocaine, no data were submitted supporting the use of these ingredients in the treatment of pain and discomfort associated with boils. Thus, the agency has determined that these ingredients (other than benzocaine) are not generally recognized as safe and effective for this use. The affected ingredients are listed in § 310.545(a)(5) (21 CFR 310.545(a)(5)). Data were submitted for benzocaine, and action on this ingredient is being deferred and transferred to a separate rulemaking for OTC external analgesic drug products.

In the ongoing rulemaking for OTC external analgesic drug products, general claims for OTC topical analgesic, anesthetic, and antipruritic active ingredients have been proposed in part 348 (48 FR 5852 at 5868, February 8, 1983). Proposed § 348.50(b)(2) would establish the temporary relief of pain, itching, or pain and itching as an intended use. The proposed labeling would also allow a description of several conditions that pain and itching are associated with, e.g., sunburn, insect bites, and minor skin irritations. Section 348.50(b) also includes proposed labeling for other specialized uses of analgesic, anesthetic, and antipruritic ingredients. See, e.g., proposed § 348.50(b)(5) for products used for the treatment of fever blisters and cold sores. (See 55 FR 3370 at 3382 and 3383, January 31, 1990.) The agency has determined that the appropriate place to include relief of the pain and itching of boils, if supported by appropriate data, would be proposed § 348.50(b). Accordingly, the agency is deferring a decision on benzocaine as a topical analgesic, anesthetic, and antipruritic active ingredient for relief of pain and discomfort of boils. That use of benzocaine will be discussed in the

ext[illegible]nalgesic drug rulemaking in a future issue of the **Federal Register**. Products containing benzocaine labeled for the temporary relief of pain and discomfort of boils may continue to be marketed at this time.

This final rule declares OTC drug products containing active ingredients for the treatment of boils to be new drugs under section 201(p) of the act, for which an application or abbreviated application (hereinafter called application) approved under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 is required for marketing. In the absence of an approved application, products containing drugs for this use also would be misbranded under section 502 of the act (21 U.S.C. 352). In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application.

This final rule amends 21 CFR part 310 to include drug products containing ingredients for the treatment of boils by adding new § 310.531 (21 CFR 310.531) to subpart E. The inclusion of OTC boil treatment drug products in part 310 follows FDA's established policy for regulations in which there are no monograph conditions. (See, e.g., §§ [illegible]0, 310.519, 310.525, 310.526, 310.532, 310.533, and 310.534.) If, in the future, any ingredient is determined to be generally recognized as safe and effective for use in an OTC boil treatment drug product, the agency will promulgate an appropriate regulation at that time.

The OTC drug procedural regulations (§ 330.10) 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 does not 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. In place of Category I, the term "monograph conditions" is used; in place of Category II or III, the term "nonmonograph conditions" is used.

[illegible]cussed in the proposed rule for O[illegible]al treatment drug products (53 FR 2198), the agency advised that it would provide a period of 12 months after the date of publication of the final monograph in the **Federal Register** for relabeling and reformulation of OTC boil treatment drug products to be in compliance with the monograph. Although data and information were submitted on ichthammol and sulfur in response to the proposed rule, they were not sufficient to support monograph conditions, and no monograph is being established at this time. Therefore, boil treatment drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions). In the advance notice of proposed rulemaking (47 FR 28306), the agency advised that conditions for the drug products subject to this monograph would be effective 6 months after the date of publication of a final monograph in the **Federal Register**. Because no OTC drug monograph is being established for this class of drug products, the agency is adopting this 6-month effective date for the nonmonograph conditions for these drug products. Therefore, on or after May 16, 1993, no OTC drug products that are subject to this final rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application.

In response to the proposed rule on OTC boil treatment drug products, one manufacturer submitted a comment and data. A copy of the comment and data received is on public display in the Dockets Management Branch (address above). Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comment

1. The comment submitted data in support of the safety and effectiveness of benzocaine in promoting reduction in boil size and relieving pain associated with boils (furuncles) (Ref. 1). As noted above, consideration of the use of benzocaine for relief of pain associated with boils is transferred to the rulemaking for OTC external analgesic drug products. The agency is only reviewing the data as they relate to reduction in boil size in this final rule. Three studies (Florendo, Weinrauch, and Goldstein) having identical protocols were submitted. The protocol for each study prescribed a randomized, double-blind, vehicle-controlled study enrolling 30 to 50 subjects with a clinical diagnosis of boils. The active treatment contained two active ingredients, benzocaine (20 percent) and triclosan (0.35 percent), while the vehicle was stated to contain triclosan (0.25 percent) only. Subjects were examined in a dermatology clinic or private office where a clinical history was obtained and the baseline boil size was determined. Subjects were then randomly assigned to a treatment group and told to apply the medication twice daily, in the morning and evening. The first application was given in the office or clinic. Reduction in boil size was one efficacy measure in these studies. Boil size determination was supposed to be made when pain relief was first experienced and after 3 days of treatment. Reduction in boil size was the difference in diameter of the boil between baseline and the end of treatment. Change in boil diameter, percent reduction in boil diameter, and the percent of subjects with a reduction in boil size were compared for the two treatments.

The agency has determined that the data are inadequate to demonstrate benzocaine's effectiveness in reducing the size of a boil. The agency considers the study design as having a number of problems. The active treatment was a combination product with two active ingredients. To prove efficacy, a four-arm study (to include each ingredient, the combination product, and vehicle) should have been conducted. The submitted studies had no true placebo (vehicle) because the vehicle component contained triclosan 0.25 percent, a concentration 0.1 percent less than used in the active treatment. Even though this concentration is lower than that of triclosan in the active treatment, it still may have contributed to the study results because it can have antibacterial properties. Thus, beneficial results of the active treatment may have been attributable to one or both of the two active ingredients. To prove efficacy for benzocaine, a study should compare benzocaine to its vehicle without triclosan. The submitted study design was only a test of whether the combination of benzocaine and triclosan outperforms triclosan by itself in the treatment of boils. The study design did not exclude any possible beneficial effects resulting from the incorporation of triclosan into the active treatment or the vehicle.

Boil size measurements should have been made with accuracy and with diligence in a study which claimed, as one of its objectives, to influence the size of the baseline condition. There should have been exclusions for subjects on recent oral antibiotics and on systemic or intralesional corticosteroid treatment. Subjects with multiple boils in adjacent areas should not have been accepted into the studies. Carbuncles and furuncles behave very differently on a clinical basis, and the

former should not have been included in a study on boils. Carbuncles are not simple boils and should not have been included in a study on boils because these lesions behave differently and require either incision and drainage, antimicrobial therapy, or both (Ref. 2).

The Florendo study enrolled 52 subjects: 24 subjects were randomized to the placebo group, and 28 subjects were randomized to the active group. Followup data were obtained from all 52 subjects. The two treatment groups were similar with respect to sex, age, and the age and size of boils. The treatment group did have a significantly higher proportion of subjects with boils which oozed or burst than did the placebo group. Four subjects in the treatment group and five subjects in the placebo group had multiple boils. The sponsor analyzed the change in boil size both with the boil as the unit of analysis and with the person as the unit of analysis. In the latter analysis, changes in boil size were first averaged within each person.

In the sponsor's analysis, a significantly higher percentage of treatment subjects than vehicle subjects had a reduction in boil size ($p < .05$); this was true whether the analysis was by subject or by boil and whether or not boils which burst were excluded. The mean absolute reduction in boil size was greater in the treatment group than in the vehicle group in all analyses. Borderline significance was achieved ($p < .06$) in the two analyses with all boils included (whether analyzed by boil or by person). Similar findings were achieved with percentage change in boil size. The agency notes that the size of the boils was measured only to the nearest centimeter (cm). The agency believes that a more exact measurement should have been made to assess changes in size.

The Weinrauch study enrolled 51 subjects: 27 subjects were randomized to the placebo group, and 24 subjects were randomized to the treatment group. Followup data were obtained from all 51 subjects. The two treatment groups were similar with respect to sex, age, and all the baseline parameters. No subjects had multiple boils. Four boils in the vehicle group and one in the treatment group burst or oozed during the trial.

In the sponsor's analysis, when boils that burst were excluded, there was a significantly greater proportion of subjects with a reduction in boil diameter as well as a significantly greater mean absolute and percentage boil size reduction in the treatment group compared to the vehicle group. When all boils were included, the direction of these results did not change, and they did not approach statistical significance.

The Goldstein study enrolled 69 subjects, with 66 (38 vehicle and 28 treatment) subjects completing it. One placebo subject was excluded because his boil size was not initially recorded. Also, one subject was on another medication, which was a violation of the protocol. The two treatment groups were similar with respect to age and the baseline parameters. No subject had multiple boils. One boil in the treatment and one boil in the vehicle group burst during the trial.

No significant differences were observed with respect to change in boil size. The vehicle group had a slightly higher proportion of subjects with reduction in boil diameter (37 percent) than did the treatment group (32 percent).

The agency found that the data sheets (Ref. 1) showed a great variation in the times when boil size was measured. For some subjects, boil size was measured only during the first 4 hours; for other subjects, measurements were made only after 1 day or 3 days. Measurements were made on both day 1 and 3 for less than half of the subjects who received the drug. The inconsistency of these measurements makes the data unsatisfactory. Also, some subjects did not complete the 3-day study; they were stopped after 1 day to begin either oral administration of antibiotics or to have incision and drainage.

The study appears not to have been conducted with proper care. Boil size was measured only to the nearest cm. Boil size was not measured precisely or consistently on all subjects in a study that proposes to study changes in boil size resulting from treatment. The boil size was not recorded for several subjects (e.g., subject 2,612). There was some confusion as to the meaning of some of the data entries; for example, terms such as "1.3" for presence of pus (subject 2,654) and "patient aspirated pus after the first day" (subject 3,577). Data entries like these cast doubt on the validity and/or appropriateness of the data recording and the subjects studied.

The raw data sheets for the Goldstein study (Ref. 1) are included in the file and contain numerous inconsistencies. At least one subject with no baseline boil size measurement was included in the analysis. In conclusion, there are numerous errors and omissions in the conduct of the Goldstein study that cause the agency to conclude that the results should be discounted.

In summary, the three studies submitted were not designed properly. The data collection for these studies appears to be incomplete in many instances. The subjects were not uniformly assessed at the various time points specified in the protocol for data collection, and the data were not collected precisely. Boil size measurements appear not to have been carried out carefully, and measurements were made in an inexact manner. The design of the studies was not appropriate for a two-component (combination) product. A four-arm study (to include each component, the combination product, and the vehicle) was needed to demonstrate efficacy. The vehicle should not have contained either component of the combination product. In conclusion, none of the three studies is an adequate, well-controlled study. Benzocaine has not been shown to be effective in reducing the size of boils.

The comment subsequently informed the agency (Ref. 3) that triclosan in a concentration of 0.35 percent was in both the vehicle and in the active drug. The comment stated that it was a typographical error stating that the concentration was 0.25 percent.

The comment contended that the active preparation was not a combination product because the triclosan in the product (as an antimicrobial) does not have proven effectiveness. The comment further argued that even if triclosan were proven effective as an antimicrobial, its "contribution" as an inactive ingredient is irrelevant to the results. The comment maintained that the only active ingredient was benzocaine, whose efficacy for relief of pain was proven. The comment claimed that triclosan had two purposes in the product: (1) To help guard against spread of infection from a boil to other sites if the boil ruptured, and (2) to act as a bacteriostatic preservative.

Based on the comment's arguments (Ref. 3), the agency is now treating the comment as addressing only the claim that benzocaine is effective for relief of pain associated with boils, and that the comment is not interested in other claims being attributed to other ingredients used to treat boils. As noted above, the use of benzocaine for relieving pain associated with boils is being transferred to the rulemaking for OTC external analgesic drug products.

References

(1) Comment No. C4, Docket No. 82N-0054, Dockets Management Branch.

(2) Maibach, H. I., R. Aly, and W. Noble, "Bacterial Infections of the Skin" in Dermatology, 2d ed., edited by Moschella, S., and H. Hurley, W. B. Saunders Co., Philadelphia, pp. 612–613, 1985.

(3) Comment No. C5, Docket No. 82N–0054, Dockets Management Branch.

2. The comment included data in support of the usefulness of the ingredients ichthammol, sulfur, and triclosan in a combination product for the treatment of boils (Refs. 1 through 5). The comment also urged the agency to consider benzocaine in combination with ichthammol, sulfur, and triclosan used as antimicrobials for the treatment of boils.

The agency has reviewed the data submitted on ichthammol, sulfur, and triclosan as antimicrobials for the treatment of boils and finds they are inadequate to establish effectiveness for this use. Of the references submitted with the comment, the agency considers the following pertinent to ichthammol and sulfur: Kownatzki, Urich, and Schopf (Ref. 2) showed that ichthyol (ichthammol) induced a neutrophilic cell accumulation in an in vitro chemotaxis (Boyden) chamber. On this basis, they concluded that ichthyol has anti-inflammatory properties. Libenson et al. (Ref. 3) concluded from a laboratory experiment that elemental sulfur has antibacterial activity against reptococcal strains and to a lesser gree against *Staphylococcus aureus*. oiwood (Ref. 4) concluded by an in vitro test that colloidal sulfur has antistaphylococcal activity in an experimental inoculation medium.

The agency finds that these references demonstrate that in laboratory (in vitro) experimental testing, ichthammol and sulfur possess certain properties that might make them useful in certain inflammatory and bacteriological conditions. However, the references submitted did not contain any human clinical studies on the use of ichthammol and sulfur for the treatment of boils. Thus, the references do not contain adequate data to establish that ichthammol and sulfur are safe and effective in the treatment of boils. The agency notes that, after the initial submission was made, the comment subsequently stated that triclosan at 0.35 percent does not have proven effectiveness as an antimicrobial (Ref. 5). The agency concludes that data from well-controlled human clinical studies are necessary to demonstrate the safety and efficacy of ichthammol, sulfur, or triclosan as antimicrobials useful for the treatment of boils. Likewise, clinical data are also needed to support any nbination of ichthammol, sulfur, or closan with benzocaine.

References

(1) Comment No. C4, Docket No. 82N–0054, Dockets Management Branch.

(2) Kownatzki, E., S. Urich, and E. Schopf, "The Effect of a Sulfonated Shale Oil Extract (Ichthyol) on the Migration of Human Neutrophilic Granulocytes *in vitro*," Archives of Dermatological Research, 276:235–239, 1984, in Comment No. C4, vol. 3, exhibit J, Docket No. 82N–0054, Dockets Management Branch.

(3) Libenson, L. et al., "Antibacterial Effect of Elemental Sulfur," Journal of Infectious Diseases, 93:28–35, 1953, in Comment No. C4, vol. 3, exhibit J, Docket No. 82N–0054, Dockets Management Branch.

(4) Woiwood, A. J., "The Inhibition of Bacterial Growth by Colloidal Heavy Metal Sulphides and by Colloidal Sulphur," Journal of General Microbiology, 10:509–520, 1954, in Comment No. C4, vol. 3, exhibit J, Docket No. 82N–0054, Dockets Management Branch.

(5) Comment No. C5, Docket No. 82N–0054, Dockets Management Branch.

3. The comment urged the agency to consider ichthammol and sulfur as "drawing" agents alone or in combination with benzocaine. The comment submitted a large number of published references on these ingredients (Ref. 1) together with the data on benzocaine (Ref. 2) discussed in comment 1 of section I. of this document.

The agency has reviewed the references and finds they are inadequate to establish the safety and effectiveness of ichthammol or sulfur for use as a drawing agent to treat boils. Five of the references (Refs. 3 through 7) discussed ichthammol and sulfur for various indications when applied topically, but none of the references specifically discussed the use of ichthammol, sulfur, or any ingredient as a "drawing" agent. The creation of an osmotic equilibrium is postulated as the mechanism of action for drawing salves and is discussed in comment 5 of section I. of this document below. In the advance notice of proposed rulemaking on OTC boil ointment drug products, the Panel concluded that drawing salves to treat boils do not have any merit (47 FR 28308 at 28308). The agency concludes that the data submitted are not adequate to support the effectiveness of ichthammol and sulfur as "drawing" agents individually or in combination with benzocaine in treating or in reducing the size of a boil. Data from well-controlled human clinical studies are necessary to demonstrate the safety and effectiveness of ichthammol or sulfur for use as a "drawing" agent in the treatment of boils.

References

(1) Comment No. C4, vol. 3, exhibit J, Docket No. 82N–0054, Dockets Management Branch.

(2) Comment No. C4, Docket No. 82N–0054, Dockets Management Branch.

(3) Kownatzki, E., S. Urich, and E. Schopf, "The Effect of a Sulfonated Shale Oil Extract (Ichthyol) on the Migration of Human Neutrophilic Granulocytes in vitro," Archives of Dermatological Research, 276:235–239, 1984, in Comment No. C4, vol. 3, exhibit J, Docket No. 82N–0054, Dockets Management Branch.

(4) Libenson, L. et al., "Antibacterial Effect of Elemental Sulfur," Journal of Infectious Diseases, 93:28–35, 1953, in Comment No. C4, vol. 3, exhibit J, Docket No. 82N–0054, Dockets Management Branch.

(5) Woiwood, A. J., "The Inhibition of Bacterial Growth by Colloidal Heavy Metal Sulphides and by Colloidal Sulphur," Journal of General Microbiology, 10:509–520, 1954, in Comment No. C4, vol. 3, exhibit J, Docket No. 82N–0054, Dockets Management Branch.

(6) Czarnetzki, B. M., "Inhibitory Effects of Shale Oils (Ichthyols) on the Secretion of Chemotactic Leukotrienes From Human Leukocytes and on Leukocyte Migration," The Journal of Investigative Dermatology, 87:694–697, 1986, in Comment No. C4, vol. 3, exhibit J, Docket No. 82N–0054, Dockets Management Branch.

(7) Combes, F. C., "The Role of Sulfur in Dermatology," New York State Journal of Medicine, 32:1019–1023, 1932, in Comment No. C4, vol. 3, Exhibit J, Docket No. 82N–0054, Dockets Management Branch.

4. The comment noted the agency's statement in the tentative final monograph (53 FR 2198 at 2204) that "the 'drawing' action of ingredients such as magnesium sulfate or ichthammol * * * needs to be shown clinically." The comment stated that, as it understood this statement, clinical proof of any "drawing" action for benzocaine will not be required.

The comment is correct in stating that clinical proof of any "drawing" action for benzocaine is not required. No claim as a "drawing" agent has been attributed to benzocaine. Thus, the statement in the tentative final monograph on "drawing" action of ingredients such as magnesium sulfate or ichthammol did not include benzocaine. However, if a claim for "drawing" action were to be made for benzocaine, then clinical proof would be required.

5. The comment contended that magnesium sulfate and ichthammol in a boil ointment formula contribute to a "drawing" action. The comment suggested that such an action "is related to the osmotic equilibrium created at the site of application, i.e., the high fluid level of the boil versus the high solids level of the formula." The comment maintained that over a period of time and as the boil increases in fluid volume, this fluid will favor the salve formula and a decrease in boil volume will result. The comment reasoned that the "drawing" action results because the magnesium sulfate and ichthammol upset the equilibrium between the fluid

in the boil and the formula containing these and other base ingredients on the surface outside the boil.

The agency acknowledges the comment's contention and theory concerning a "drawing" action for magnesium sulfate and ichthammol. However, the comment did not submit adequate effectiveness data to support a "drawing" action for magnesium sulfate or ichthammol in the treatment of boils. The agency reviewed and evaluated the comment's submitted literature references (see comment 3 of section I. of this document) and found those references inadequate to support the effectiveness of any ingredient as a "drawing" agent.

II. The Agency's Final Conclusions on OTC Boil Treatment Drug Products

At this time, there is a lack of data from adequate and well-controlled, double-blind studies to establish that benzocaine, ichthammol, magnesium sulfate, sulfur, triclosan, or any other ingredients are effective to treat or reduce the size of boils. The agency has determined that no active ingredient has been found to be generally recognized as safe and effective for this OTC use. Treatment is defined as reducing the size of a boil or reducing an infection related to a boil. Treatment has involved the use of "drawing salves" for these purposes. These "drawing salves" contained various ingredients.

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule in part 310 establishing that certain active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective. That final rule was effective on May 7, 1991, and included in § 310.545(a)(5) the following ingredients that had been previously considered under this rulemaking for use in the treatment of boils: Aminoacridine hydrochloride, bismuth subnitrate, calomel, camphor, cholesterol, ergot fluidextract, hexachlorophene, isobutamben, juniper tar, lanolin, magnesium sulfate, menthol, methyl salicylate, oxyguinoline sulfate, petrolatum, phenol, pine tar, rosin, rosin cerate, sassafras oil, thymol, and zinc oxide. The final rule in this document establishes that any OTC boil treatment drug product is not generally recognized as safe and effective and expands the nonmonograph ingredients to include all other active ingredients for the treatment of boils, such as benzocaine, ichthammol, sulfur, and triclosan. Therefore, any ingredient that is labeled, represented, or promoted for OTC use for the treatment of boils is considered nonmonograph and misbranded under section 502 of the act and is a new drug under section 201(p) of the act for which an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 of the regulations is required for marketing. In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application. Any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action. In order to avoid duplication in listing OTC boil treatment active ingredients in more than one regulation and for ease in locating these ingredients in the Code of Federal Regulations, the agency is listing all of these ingredients in a single regulation in new § 310.531 entitled "Drug products containing active ingredients offered over-the-counter (OTC) for the treatment of boils." Accordingly, the ingredients currently listed in § 310.545(a)(5) are now being listed in § 310.531(d), and § 310.545(a)(5) is being removed. The additional ingredients covered by this final rule are being listed in § 310.531(e). This final rule does not apply to OTC drug products that contain benzocaine and that are labeled for the temporary relief of itch, pain, and discomfort of boils. The agency is deferring that use of benzocaine to the rulemaking on OTC external analgesic drug products. A paragraph is included in new § 310.531 to indicate that section does not apply to drug products that contain benzocaine labeled, represented, or promoted for OTC topical use with such external analgesic claims.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (53 FR 2198 at 2205). The agency has examined the economic consequences of this final rule 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 final rule for OTC boil treatment 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 treatment drug products is not expected to pose such an impact on small businesses because only a limited number of products are affected. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

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

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.531 is added to subpart E to read as follows:

§ 310.531 Drug products containing active ingredients offered over-the-counter (OTC) for the treatment of boils.

(a) Aminacrine hydrochloride, benzocaine, bismuth subnitrate, calomel, camphor, cholesterol, ergot fluid extract, hexachlorophene, ichthammol, isobutamben, juniper tar (oil of cade), lanolin, magnesium sulfate, menthol, methyl salicylate, oxyguinoline sulfate, petrolatum, phenol, pine tar, rosin, rosin cerate,

as oil, sulfur, thymol, triclosan, ic oxide have been present in OTC boil treatment drug products. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredient for OTC use for the treatment of boils. Treatment is defined as reducing the size of a boil or reducing an infection related to a boil. Treatment has involved the use of "drawing salves" for these purposes. These "drawing salves" contained various ingredients. Based on evidence currently available, any OTC drug product offered for the treatment of boils cannot be considered generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted for the treatment of boils is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any OTC boil treatment drug product is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After May 7, 1991, any such OTC drug product that contains aminacrine hydrochloride, bismuth subnitrate, calomel, camphor, cholesterol, ergot fluid extract, hexachlorophene, isobutamben, juniper tar (oil of cade), lanolin, magnesium sulfate, menthol, methyl salicylate, oxyguinoline sulfate, petrolatum, phenol, pine tar, rosin, rosin cerate, sassafras oil, thymol, or zinc oxide initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

(e) After May 16, 1994, any such OTC drug product that contains benzocaine, ichthammol, sulfur, or triclosan initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

(f) This section does not apply to drug products that contain benzocaine labeled, represented, or promoted for OTC topical use in accordance with part 348 of this chapter.

§ 310.545 [Amended]

3. Section 310.545 *Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses* is amended by removing and reserving paragraph (a)(5).

Dated: November 8, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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