DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 333 and 369

[Docket No. 75N-183F]

RIN 0905-AA06

Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for First Aid Antiseptic Drug Products

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of an amended tentative final monograph that would establish conditions under which over-the-counter (OTC) first aid antiseptic drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking to amend the previous notice of proposed rulemaking on topical antimicrobial drug products after considering that rulemaking and public comments on it. (See the Federal Register of January 6, 1978, 43 FR 1210.) 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 January 21, 1992. Because of the length and complexity of this proposed regulation, the agency is allowing a period of 180 days for comments and objections instead of the normal 60 days. New data by July 22, 1992. Comments on the new data by September 22, 1992. Written comments on the agency's economic impact determination by January 21, 1992.

ADDRESSES: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

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

SUPPLEMENTARY INFORMATION: In the Federal Register of September 13, 1974 (39 FR 33103), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC topical antimicrobial drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Antimicrobial I Drug Products (Antimicrobial I 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 November 12, 1974. Reply comments in response to comments filed in the initial comment period could be submitted by December 12, 1974. In response to numerous requests, the agency issued a notice in the Federal Register of October 17, 1974 (39 FR 37066) granting an extension of the deadline for comments until December 12, 1974, and for reply comments until January 13, 1975.

In the Federal Register of January 6, 1978 (43 FR 1210), FDA published, under § 330.10(a) (7), a notice of proposed rulemaking to establish a monograph for OTC topical antimicrobial drug products, based on the recommendations of the Antimicrobial I Panel and the agency's response to comments submitted following publication of the advance notice of proposed rulemaking.

Interested persons were invited to submit objections or requests for oral hearing by February 6, 1978. In response to numerous requests to extend the time period for submitting objections or requests for oral hearing, the agency issued a notice in the Federal Register of February 3, 1978 (43 FR 4637) granting an extension of the deadline to March 6, 1978.

During this time period, the agency received 6 petitions that requested reopening the administrative record and 11 requests for an oral hearing. In a notice published in the Federal Register of March 9, 1979 (44 FR 13041), the agency deferred action on the requests for a hearing, but granted the petitions to reopen the record to allow interested persons to submit comments and any new or additional data by June 7, 1979, and reply comments by July 9, 1979. FDA also stated its intent to publish an updated (amended) tentative final monograph based on the review and evaluation of new submissions and a reevaluation of existing data.

In a notice published in the Federal Register of October 26, 1979 (44 FR 61609), the agency again reopened the administrative record for the submission of new data by March 26, 1980, and for comments on the new data by May 27, 1980. This action was taken to permit manufacturers to submit the results of testing to FDA as expeditiously as possible prior to establishment of a final monograph.

Subsequent to the June 7, 1979 closing date for the submission of new data, and prior to the October 26, 1979 reopening of the administrative record, data and information were submitted to FDA. In a notice published in the Federal Register of March 21, 1980 (45 FR 18398), the agency advised that it had reopened the administrative record for OTC topical antimicrobial drug products to allow for consideration of data and information that had been filed in the Dockets Management Branch after the administrative record on the tentative final monograph had officially closed on March 6, 1978. The agency concluded that any new data and information filed prior to March 21, 1980 should be available to the agency in developing a proposed regulation in the form of a tentative final monograph.

In a notice published in the Federal Register on January 5, 1982 (47 FR 436), the agency advised that it had again reopened the administrative record for OTC topical antimicrobial drug products to allow for consideration of the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) on mercury-containing drug products. Interested persons were invited to submit comments by April 5, 1982, and reply comments by May 5, 1982. FDA stated that the proceeding to develop a monograph for mercury-containing drug products would be merged with the general proceeding to establish a monograph for OTC topical antimicrobial drug products.

In a notice published in the Federal Register on May 21, 1982 (47 FR 22324), the agency advised that it had again reopened the administrative record for OTC topical antimicrobial drug products to allow for consideration of the recommendations of the Miscellaneous External Panel on alcohol drug products. Interested persons were invited to submit comments by August 19, 1982, and reply comments by September 20, 1982. The notice stated that the proceeding to develop a monograph for alcohol drug products would be merged with the general proceeding to establish a monograph for OTC topical antimicrobial drug products.

In the Federal Register of September 7, 1982 (47 FR 39406), FDA issued a notice to reopen the administrative record for OTC topical antimicrobial drug products to allow for consideration of the Miscellaneous External Panel's recommendations on topical antimicrobial drug products used for the treatment of diaper rash. The agency discussed topical antimicrobial active

ingredients for this use in the **Federal Register** of June 20, 1990 (55 FR 25246).

In accordance with § 330.10(a)(10), the data and information considered by the Panels were put on public display in the Dockets Management Branch (address above), after deletion of a small amount of trade secret information. In response to the previous tentative final monograph and the advance notice of proposed rulemaking for mercury-containing drug products and the advance notice of proposed rulemaking for alcohol drug products, 4 drug manufacturers' associations, 44 drug manufacturers, 1 medical device manufacturer, 1 drug distributor, 2 medical schools, 2 research laboratories, 1 law firm, and 1 consulting firm submitted comments. Copies of the comments received are also on public display in the Dockets Management Branch (address above).

The advance notice of proposed rulemaking, which was published in the **Federal Register** of September 13, 1974 (39 FR 33103), was designated as a "proposed monograph" in order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10). Similarly, the notice of proposed rulemaking, which was published in the **Federal Register** of January 6, 1978 (43 FR 1210), was designated as a "tentative final monograph." The present document is also designated as a "tentative final monograph." The legal status of each tentative final monograph, however, is that of a proposed rule.

This antimicrobial rulemaking is broad in scope, encompassing products that may contain the same active ingredients, but are labeled and marketed for different intended uses. For example, one group of products is primarily used by consumers for "first aid" and includes skin antiseptics, skin wound cleansers, and skin wound protectants. Another group of products is used by consumers on a more frequent, even daily basis, and includes products for personal use in the home, such as when caring for invalids and during family illness. Still a third group of products is generally intended for use by health professionals and includes health-care personnel handwashes, patient preoperative skin preparations, and surgical hand scrubs.

In order to expedite the completion of the first aid section of the antimicrobial monograph, the agency is publishing a separate tentative final monograph for these products. The non-first aid uses of topical antimicrobials will be addressed in a future issue of the **Federal Register**. Although the amended tentative final monographs for first-aid antiseptics and non-first aid uses of topical antimicrobials are being published separately, both categories will eventually be included under part 333 (21 CFR part 333).

The agency also has decided that OTC topical antimicrobial and topical antibiotic drug products should be included within the same monograph. Although an advance notice of proposed rulemaking to establish a monograph for OTC topical antibiotic drug products was published under part 342 (21 CFR part 342) on April 1, 1977 (42 FR 17642), the final monograph for those products was issued on December 11, 1987 (52 FR 47312) as a new subpart of the OTC topical antimicrobial monograph, 21 CFR part 333 subpart B—First Aid Antibiotic Drug Products.

Subpart A will cover first aid antiseptic drug products; subpart C will cover antifungal drug products; subpart D will cover acne drug products; and subpart E will cover non-first aid uses of topical antimicrobial drug products.

In this tentative final monograph (proposed rule) to establish subpart A of part 333 (21 CFR part 333), FDA states its position on the establishment of a monograph for OTC first aid antiseptic drug products only. This document addresses only those comments and data concerning the previous antimicrobial tentative final monograph that are related to "first aid uses." The agency will address all other submitted information at a later date.

This proposal constitutes FDA's reevaluation of the January 6, 1978 tentative final monograph based on the comments received and the agency's independent evaluation of the Miscellaneous External Panel's reports on OTC alcohol and mercury-containing drug products and the comments received. The following sections of the January 6, 1978 tentative final monograph for topical antimicrobial drug products are being addressed in this document: §§ 333.1, 333.3, 333.20, 333.40, 333.45, 333.65, 333.80, 333.90, 333.92, and 333.93. The following sections of the advance notice of proposed rulemaking for alcohol drug products are being addressed in this document: §§ 333.55 and 333.98. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them. (See Part I.)

The OTC drug 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 for OTC topical antimicrobial drug products (39 FR 33103), the agency suggested that the conditions included in the monograph (Category I) be effective 30 days after the date of publication of the final monograph in the **Federal Register** and that the conditions excluded from the monograph (Category II) be eliminated from OTC drug products effective 6 months after the date of publication of the final monograph, regardless of

whether further testing was undertaken to justify their future use. 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 30 days 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 these 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.

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 January 7, 1972 (37 FR 235) 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 (address above).

I. The Agency's Tentative Conclusions on the Comments and Reply Comments

A. General Comments

1. Two comments contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. One comment referred to statements on this issue submitted earlier to other OTC rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464 at 9471 to 9472), and in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by informal rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–698 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. Two comments expressed concern over the amount of time that would be allowed for the relabeling of products after publication of the final monograph, citing the "Statement of Inflation Impact Potential" for the tentative final monograph which allowed a period of 7 to 12 months for manufacturers to implement labeling changes. One of the comments stated that the final monograph should allow at least 12 months to implement any required labeling changes. The other comment stated that such a period would be adequate for most regular production items, but would place a hardship on manufacturers with respect to infrequently produced products (e.g., once a year) and slow-moving items. This comment suggested an approach that would require all new labels ordered to comply in 6 months, all labels placed on products to comply in 18 months, and labels on all products shipped to comply in 24 months. The comment stated that this approach would allow labeling inventories for infrequently produced and slow-moving items to be depleted and would accommodate the agency's objectives and minimize the cost burden imposed on manufacturers and ultimately on consumers.

The agency agrees that a reasonable period of time should be provided for relabeling. As discussed more fully in the preamble of this document, the agency is proposing to extend this period so that the final monograph will be effective 12 months after the date of its publication in the **Federal Register**. The agency believes that, within this time, most manufacturers can have their products, including those infrequently produced, in compliance with the final monograph.

3. One comment expressed concern that scientific interpretations of testing data may differ between pharmaceutical manufacturers and FDA staff. The comment requested that the OTC drug review procedures provide an opportunity for a hearing prior to a final decision on a petition to reclassify an OTC drug product from Category III to Category I when genuine factual or scientific issues are raised concerning a drug's conformity with an OTC drug monograph.

This comment was submitted before the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). Before this decision was rendered, the OTC drug review procedural regulations in 21 CFR 333.10 allowed the continued marketing and testing of a Category III condition after a final monograph had been issued. Because of the court decision in *Cutler* v. *Kennedy*, the agency revised the OTC drug review procedural regulations so that all Category III testing must be completed prior to publication of a final monograph, if a manufacturer wants to upgrade a condition to Category I before the establishment of a final monograph. (See "Revision of Procedures Relating to Category III; Final Rule," published in the **Federal Register** of September 29, 1981, 46 FR 47730.)

Along with the publication of these revised procedures, the agency published a policy statement that provides for an exchange of information, including agency "feedback," on Category III test data between the agency and pharmaceutical manufacturers prior to publication of a final monograph. (See "Over-the-Counter (OTC) Drug Review Policy Statement," published in the **Federal Register** of September 29, 1981, 46 FR 47740.) The agency acknowledges that scientific interpretations of testing data may differ and believes that this "feedback" policy affords an adequate mechanism for pharmaceutical manufacturers and FDA to discuss air interpretations of testing data prior to a final monograph. In addition, under § 330.10(a)(7) interested parties may request an oral hearing after publication of a tentative final monograph. The agency believes that the existing regulations and the new "feedback"

policy provide adequate opportunities for pharmaceutical manufacturers to discuss data interpretations with FDA.

4. One comment stated that the agency should initiate revocation of new drug applications (NDA's) for products covered by the antimicrobial monograph upon publication of the final monograph. The comment contended that this would end continued use of claims that were approved under the NDA but are prohibited by the monograph, thus avoiding inequities in the industry and confusion in the marketplace.

The agency agrees with the comment that inequities and confusion should be avoided. After a final rule for OTC first aid antiseptic drug products is published, but before it becomes effective, the agency intends to publish in the **Federal Register** a notice of opportunity for hearing on a proposal to withdraw approval of new drug applications for products within the scope of the final monograph for OTC antimicrobial drug products.

5. One comment requested that Category III drugs be placed in Category I because they have already been extensively tested and have long been proven in the marketplace. According to the comment, if manufacturers consider it economically unfeasible to conduct the extensive Category III tests (43 FR 1210 at 1239 to 1245) the public would subsequently be deprived of drugs that it has found beneficial for self-medication for many decades. The comment stated that any currently marketed OTC drug that may later be proven unsafe, or whose claimed indications may be shown to be unwarranted, may be properly placed in Category II. However, the comment concluded that OTC drugs for which the Panel or the agency is merely seeking additional data should not be deleted from Category I while such data are being sought.

If the agency has classified an ingredient in Category III, it is because the available data are insufficient to classify the ingredient as generally recognized as safe and effective. Such ingredients cannot appropriately be put in Category I unless sufficient additional data are submitted to the rulemaking. This comment was submitted before the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979), in which the OTC drug review procedural regulations in 21 CFR 333.10 that allowed the continued marketing and testing of a Category III condition after a final monograph were declared invalid. As stated in comment 3, because of this court decision, the agency has revised the OTC drug review procedural regulations so that all Category III testing must be completed prior to publication of a final monograph. Thus, it is not possible for the agency to affirmatively permit Category III drugs, which will be considered nonmonograph conditions, to remain on the market after the final monograph becomes effective, even if additional testing is being conducted to obtain data to support a Category I or monograph classification.

6. One comment stated that "removal from the marketplace of products which have been placed in Category II such as iodine, and the failure to include in the monograph various substances that have proven themselves in the marketplace for many years, will inevitably require the public to resort to more expensive but unnecessary substitutes."

The agency is proposing that several OTC topical antimicrobial ingredients, which have been in the marketplace for many years, be reclassified as Category I in this tentative final monograph under the new category "first aid antiseptic." Thus, these ingredients, including iodine, would not have to be removed from the marketplace. Previously marketed ingredients that have not been demonstrated to be safe and effective for any OTC use and that, therefore, are not included in any OTC drug monograph cannot legally be marketed without an approved application. The economic impact of this amended proposed rule on first aid antiseptic drug products is discussed elsewhere in this document.

7. One commenter pointed out that under "Subpart B—Active Ingredients" of the 1978 tentative final monograph, no CFR part number was assigned to the category "skin antiseptic." However, part numbers were assigned to other categories without any Category I ingredients, with the term "reserved" in parentheses. The comment requested that this omission be corrected in the amended tentative final monograph.

The omission pointed out by the comment was an oversight. However, it is no longer necessary to assign a CFR part number to the category "skin antiseptic," because skin antiseptics have been included in the broader category identified in this tentative final monograph as first aid antiseptics. (See comment 13.) All Category I first aid antiseptic active ingredients have been listed in the amended tentative final monograph under subpart A, § 333.10.

8. One comment submitted the final report of a 24-month study on the chronic toxicity of triclocarban as a petition to reopen the administrative record. Several comments had previously requested an extension of time from the March 26, 1980 deadline for the closing of the administrative record for submission of new data on conditions classified in Category III in the tentative final order, stating that the submission of the final report on the ongoing 2-year triclocarban toxicity study would not be completed by this deadline. The comments requested that the deadline for submission of new data be extended until the submission of this final report or, in the alternative, that FDA assure that the final report would be accepted and considered in this amended tentative final monograph.

In the notice of proposed rulemaking (43 FR 1210 at 1233), the agency requested that a 24-month study on the chronic toxicity of triclocarban be repeated. In response to this request, another 24-month study was initiated promptly, but because of the 2-year duration of the study, the final report was not submitted to the agency until May 27, 1981. To make this amended notice of proposed rulemaking as complete as possible, the agency has included the final report of the study in the administrative record and has considered the results of this study elsewhere in this document. (See comment 47.) Thus, the comment's request to extend the deadline for the submission of new data relating to triclocarban has been granted.

B. General Comments on Antimicrobials

9. Several comments objected to some of the specific statements of identity, e.g., "skin wound cleanser," "skin wound protectant," and "skin antiseptic." One comment stated that the word "skin" was superfluous because all OTC antiseptics are intended only for use on the skin. Another comment contended that the statement of identity "antiseptic" is preferable to "skin antiseptic" because these products are used on cuts, scratches, and mucous membranes as well as skin. One comment questioned whether consumers understand the statement of identity "skin wound protectant" and recommended that FDA adopt more familiar terminology, such as "first aid product." Other comments requested that Category I skin wound cleansers or skin wound protectants that contain antimicrobial ingredients be allowed a statement of identity that recognizes their antimicrobial activity, such as "first aid skin antiseptic," "minor antiseptic," "mild antiseptic," or "antimicrobial skin wound cleanser."

Based upon the comments, the agency believes that more familiar terminology could be used as the statement of identity and that the word "skin" should

not be required in the statement of identity for these products. In reviewing the indications recommended by the Panel for skin antiseptics, skin wound protectants, and skin wound cleansers, the agency identified the phrase "first aid product" as common to these drug categories. "First aid" is also a term that is frequently included in the labeling of OTC topical antiseptic drug products, reflects the intended OTC use of these products, is more familiar terminology to consumers, and is readily understood by consumers. Therefore, the agency is proposing the term "first aid antiseptic" as the statement of identity for OTC topical antimicrobial active ingredients included in this tentative final monograph. The agency has no objection to the statement "first aid antiseptic for the skin" or "first aid skin antiseptic" appearing elsewhere in the labeling of these products as additional information to the consumer, provided it does not appear in any portion of the labeling required by the monograph and does not detract from such required information.

10. Several comments argued that antimicrobial soap products making cosmetic claims only are not subject to regulation as OTC drugs and should not be considered in a review of drug effectiveness. The comments contended that if the intended use of antimicrobial soaps is stated solely in terms of deodorant effect, these products are not properly subject to regulation as OTC drugs. In addition, the comments stated that the OTC drug labeling requirements for antimicrobial soaps are unduly restrictive and uninformative. One comment pointed out that prior FDA regulations have recognized that personal cleanliness products (including both soaps and detergents) and underarm deodorants are cosmetic products, citing 21 CFR 720.49(c) (10) and FDA Trade Correspondence TC–26, February 9, 1940.

Some comments objected to the requirement that microbial reduction be established to demonstrate the deodorant effectiveness of OTC antimicrobial soaps because a direct correlation between bacterial reduction and the reduction of body odor has not been scientifically determined. One comment cited three studies (Refs. 1, 2, and 3) to support this contention. The comments requested that the final antimicrobial monograph apply only to antimicrobial soaps that make specific drug claims that any reference to deodorant claims be deleted from the monograph.

Other comments requested that the labeling for antimicrobial soaps be expanded to give more emphasis to the deodorant activity of these products. The comments objected to the limitation of phrases and the restrictions on the use of the phrases "reduces odor" and "deodorant soap" as well as to phraseology concerning deodorant usage in § 333.80 of the monograph.

Several comments objected to the proposed indication "antimicrobial soap" (§ 333.80(b) (1)) and requested that it either be deleted or modified to include deodorant claims. The comments contended that it is redundant and serves no purpose to require that the label of an antimicrobial soap contain the statement "antimicrobial soap" both as an indication and as a statement of identity (§ 333.80(a)).

One comment stated that this labeling requirement represents a misuse of the word "indications" because the permitted terms "antimicrobial" or "antibacterial" do not inform consumers of the intended use of the product in terms likely to be understood by the ordinary individual. The comments stated that because these labeling requirements do not adequately convey to consumers that the principal use and benefit to be derived from the use of antimicrobial soaps is the deodorant effect, these labeling requirements may not only confuse consumers but also may deny them truthful and useful information about these products.

The agency has carefully reevaluated this issue and clarifies that the OTC drug monographs promulgated under 21 CFR part 330 cover drug ingredients and indications, not cosmetic claims. The Federal Food, Drug, and Cosmetic Act (the act) principally defines a "drug" as an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" or "intended to affect the structure or any function of the body * * *." (21 U.S.C. 321(g)(1)). The act defines a "cosmetic" as an article "intended to be rubbed, poured, sprinkled, or sprayed on, introduced into, or otherwise applied to the human body or any part thereof for cleansing, beautifying, promoting attractiveness, or altering the appearance * * *." (21 U.S.C. 321(i)(1)). The intended use of the product, therefore, determines whether the product is a "drug," a "cosmetic," or both. This intended use may be inferred from the product's labeling, promotional material, advertising, and any other relevant factor. (See, e.g., *National Nutritional Foods Association* v. *Mathews*, 557 F.2d 325, 334 (2d Cir. 1977). A manufacturer's subjective claims of intent may be pierced to find its actual intent on the basis of objective evidence. *National Nutritional Foods Association* v. *FDA*, 504 F.2d 761, 789 (2d Cir. 1974).

The agency emphasizes that the previous tentative final monograph and this amended proposal cover only those antimicrobial products that are drugs or are both drugs and cosmetics, and are not applicable to the wide variety of products that are only cosmetics but that contain antimicrobial ingredients. The agency notes that most currently marketed antimicrobial bar soaps are not viewed by the consuming public as drugs but as products providing personal cleaning and deodorizing benefits. The agency agrees that separate regulations are required to govern the safety of cosmetic products containing antimicrobial ingredients. In comment 12 of the 1978 tentative final monograph (43 FR 1210 at 1212) the agency stated its intention not to require NDA's for products containing a Category I antimicrobial ingredient at greater than preservative levels and that make no drug claims. This position remains unchanged. Therefore, the presence of an antimicrobial ingredient does not, in and of itself, make a product a drug provided that no drug claim is made. However, the antimicrobial ingredient included in a cosmetic product may not exceed the concentration provided for in an applicable monograph.

As the comments have pointed out, the agency has in the past acknowledged "deodorancy" to be a cosmetic claim. Soap products that contain antimicrobial ingredients will be considered "cosmetics," and not "drugs," if only deodorant claims (or other cosmetic claims) are made for the products. The agency has previously stated that the mere presence of an antimicrobial ingredient in a product labeled for deodorant use, with the ingredient identified only in the ingredient list and no reference to its antimicrobial properties stated elsewhere in the labeling, would not cause the product to be considered a drug (Ref. 4).

However, any broader claims that represent or suggest a drug use for the product would subject it to regulation as a drug. For example, the agency considers terms such as "antibacterial," "antimicrobial," or "kills germs" in the labeling of deodorant soap products to imply that the product will have a therapeutic effect. Such statements would constitute a drug claim for the product. Likewise, statements in the labeling of a deodorant soap product such as "antimicrobial for deodorization" or "kills germs that

cause body odor" will cause the product to be a drug. Further, the term "active ingredient(s)" used anywhere in labeling would imply that the product possesses a drug-like property and would also cause the product to be a drug.

In summary, deodorant effectiveness and related claims in the labeling of soap products that contain antimicrobial ingredients but make only cosmetic claims will not be considered further in this document. Accordingly, the agency is deleting previously proposed § 333.80. However, if a manufacturer elects to market such a product as a drug (e.g., by including labeling as an "antimicrobial"), the product is a drug and is required to demonstrate efficacy, even if the labeling claim is only for a deodorant effect. Testing guidelines for antimicrobial claims will be addressed in an amended tentative final monograph covering non-first aid topical antimicrobial indications, to be published in a future issue of the **Federal Register**.

In addition, the agency did not receive any data on the use of antimicrobial soaps specifically labeled for first aid use. Consequently, antimicrobial soaps are not being included in this tentative final monograph for this use. Other drug uses (e.g., for general health care) will also be addressed in a future issue of the **Federal Register**.

References

(1) Prince, H.N., and J.A. Rodgers, "Studies on the Aerobic Axillary Microflora Employing a Standardized Swabbing Technique (Total Counts, Speciation and Ecological Drift)," Cosmetics and Perfumery, 89:25–30, 1974.

(2) Dravnieks, A., et al., "Influence of an Antimicrobial Soap on Various Effluents From Axillae," Journal of the Society of Cosmetic Chemists, 19:611–626, 1968.

(3) Cowen, R.A., "Relative Merits of 'In Use' and Laboratory Methods for the Evaluation of Antimicrobial Products," Journal of the Society of Cosmetic Chemists, 25:307–323, 1974.

(4) Memorandum of Meeting between Armour Dial, Inc., and FDA, March 9, 1983, coded MM0001, Docket No. 75N–0183, Dockets Management Branch.

11. One comment requested that scrubbing devices, such as brushes or sponges, that are impregnated with approved antimicrobial ingredients be included in the monograph.

Although the comment intended to address professional antimicrobial uses, the question of impregnated scrubbing devices may also be relevant to first aid uses. This amended tentative final monograph does not specifically provide for the use of devices such as brushes or sponges impregnated with antimicrobials. These devices are not included in the monograph because the monograph is intended to regulate OTC drug active ingredients, not device delivery systems, except to the extent that the method of application is important to the OTC drug's safety or effectiveness, and the device employed is legally available. Under such circumstances, the monograph may specify the use of the device for the specific drug.

The agency does not believe that it is necessary to include specific references to brush or sponge delivery systems in the first aid antiseptic monograph. If a topical antimicrobial active ingredient is used to impregnate a scrubbing device such as a brush or sponge as the method of application of the drug, the topical antimicrobial component continues to be regulated as a drug (and must conform to the applicable conditions of the final monograph if the ingredient is included in the monograph for the product's labeled indications), and the instrument must satisfy the device requirements under the act. For example, a brush impregnated with an antimicrobial active ingredient and intended for use as a first aid antiseptic must conform to the first aid antiseptic requirements included in Subpart A of this proposed monograph as well as any appropriate device requirements.

12. One comment expressed concern that the tentative final monograph failed to provide consumers with an antibacterial skin cleanser for home use. The comment noted that, in addition to professional health care personnel, many consumers have a need for cleansing products containing antibacterial agents for the purpose of promoting good individual and family hygiene. Potential uses cited for such products included: (1) To reduce bacteria on the hands and face to a greater extent than can be accomplished with ordinary soap, and to prevent accumulation of bacteria from potential sources of contamination. The following examples were cited: Cleansing oneself after changing a baby's diaper, or after assisting aged or ill members of the household with their toilet needs, and before preparing a family meal. (2) The added benefit of an antibacterial cleanser for the minute cuts and abrasions from shaving and other minor traumas. (3) The need for an antibacterial cleanser other than bar soap on local parts of the body, such as the face, because soap (alkali salts of fatty acids) can be irritating or too drying for some individuals' needs. The comment recommended a new product class under proposed § 333.90(a) (skin antiseptic) to be identified as "Antimicrobial (or Antibacterial) Personal Cleanser" with claims such as "decreases bacteria on the skin" and "contains an antibacterial agent." The comment also suggested that the 10-day maximum use limitation would not be appropriate for this product class, but use could be restricted to 5 or 10 times daily.

The agency believes that the comment's recommendation has merit; however, this document is limited in scope to first aid antiseptic drug products. The agency will address the issue of cleansing products containing antibacterial agents for the purpose of promoting good individual and family health care in the non-first aid uses segment of the amended tentative final monograph, in a future issue of the **Federal Register**.

C. Comments on Definitions

13. Several comments objected to the definition of "skin antiseptic" in proposed § 333.3(f): "A nonirritating, antimicrobial-containing preparation that prevents overt skin infection." The comments asserted that this definition requires total effectiveness (that is, antimicrobial activity against all infective agents), that this is an unreasonable and unrealistic definition, and that, at present, no testing methods conclusively demonstrate total effectiveness. The comments stated that the proposed definition is too restrictive and cited three definitions of an antiseptic that do not include the concept of prevention of infection (Refs. 1, 2, and 3). In addition, the comments pointed out that the statutory definition of an antiseptic (section 201(o) of the act) is not subject to the discretionary enlargement that was recommended by the agency in the tentative final monograph (43 FR 1210 at 1215). The comments submitted alternative definitions and requested that one of them be adopted. Two comments recommended the following definition of skin antiseptic: "A nonirritating antimicrobial-containing preparation that kills or inhibits the growth of microorganisms on the skin."

As discussed earlier in this document, the agency is proposing that skin antiseptics, as well as skin wound protectants and skin wound cleansers, be included in one category called "first aid antiseptics." Thus, a separate definition of "skin antiseptic" is no longer necessary, and § 333.3(f) of the previous tentative final monograph is not being included in this amended tentative final monograph. It is generally recognized that the chief purpose of a first aid antiseptic is to kill or prevent the growth of bacteria that may cause

infection. Therefore, the agency is proposing in this amended tentative final monograph to define the term "first aid antiseptic" as follows: "An antiseptic-containing drug product applied topically to the skin to help prevent infection in minor cuts, scrapes, and burns." The agency believes this definition is consistent with section 201(o) of the act and is more realistic than the previously proposed definition because it does not require total effectiveness against all infective agents, the concern expressed by the comments.

Regarding testing, it should be noted that the Panel expressed concern over the confusion concerning the definition and use of the term "antiseptic." The Panel believed that the definition of antiseptic had been interpreted as activity against infection or microbial sepsis (39 FR 33103 at 33114). The term "antiseptic" is comparable to accepted definitions for a disinfectant. The Panel attempted to eliminate the confusion "by developing a rigorous definition of a skin antiseptic" (39 FR 33114). The Panel stated that claims stating or implying an effect against microorganisms must be supported by controlled human studies demonstrating prevention of infection. The agency indicated in the tentative final monograph (43 FR 1210 at 1211) that the testing regimens were not intended to be more burdensome than needed to prove safety and effectiveness, as required by law. However, neither the Panel nor the agency proposed a specific protocol to test claimed "skin antiseptic" products. In the tentative final monograph, the agency proposed that the testing guidelines for products intended for use by health professionals be used (43 FR 1216). The agency continues to believe that products that meet these requirements are acceptable as "first-aid antiseptics," but it is not necessary for first aid antiseptics to meet these more rigid testing requirements for products intended for use by health professionals.

In this document, the agency is proposing a more consumer-oriented indication for first aid antiseptics than the indications previously proposed in § 333.90 for skin antiseptics. The new indication is as follows: "First aid to help" [select one of the following: "prevent," ("decrease" ("the risk of" or "the chance of")), ("reduce" ("the risk of" or "the chance of")), "guard against," or "protect against"] [select one of the following: "infection," "bacterial contamination," or "skin infection"] "in minor cuts, scrapes, and burns." Manufacturers choosing to market a first aid product with this claim need only meet the requirements specified in the proposed monograph. To assist manufacturers in meeting these requirements, the agency is also providing procedures for testing a "first aid antiseptic." (See comment 56.)

References

(1) "Webster's New Collegiate Dictionary," G. and C. Merriam Co., Springfield, MA, 1975, s.v. "antiseptic."

(2) "Dorland's Illustrated Medical Dictionary," 24th Ed., W.B. Saunders Co., Philadelphia and London, 1965, s.v. "antiseptic."

(3) Harvey, S.C., "Antiseptics and Disinfectants; Fungicides; Ectoparasiticides," in "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A. Gilman, The Macmillan Co., New York, p. 988, 1975.

14. Several comments objected to the definitions of the proposed skin wound cleanser and skin wound protectant categories. One comment stated that although the Panel was only charged to evaluate antimicrobial ingredients, its recommendations for the skin wound protectants and skin wound cleansers clearly extended to nonantimicrobial ingredients. This comment recommended that FDA modify the antimicrobial monograph to make it clear that it is limited to products with antimicrobial ingredients. Two comments objected to the revision in the definition of "Skin Wound Protectant" in § 333.3(h) of the tentative final monograph, which states in part "* * * it provides a protective physical barrier and a chemical (antimicrobial) barrier * * *." The comments contended that the Panel's definition of skin wound protectant in § 333.3(f) should be adopted: "A safe, non-irritating preparation applied to small cleansed wounds which provides a protective (physical and/or chemical) barrier and neither delays healing nor favors the of micro-organisms."

One comment requested that FDA include recommendations on the safety and effectiveness of the nonantimicrobial ingredients that act as physical barriers in skin wound protectants. Another comment submitted data on a cream physical barrier product without a claimed active antimicrobial agent to show that the product is safe and nonirritating, provides a protective barrier, does not delay wound healing or favor the growth of microorganisms, and therefore meets all of the criteria for a skin wound protectant as defined by the Panel (Ref. 1). This comment argued that the addition of an antimicrobial ingredient cannot contribute to the claimed effectiveness of this product when all of the efficacy criteria have been met without it. The comment concluded that FDA should either return to the Panel's definition, which does not require a chemical barrier, or modify the definition and testing required for a skin wound protectant in the previous tentative final monograph in such a way that the antimicrobial ingredient will contribute to the claimed efficacy of the product.

The agency agrees with the comment that contended that skin wound cleansers and skin wound protectants without active antimicrobial ingredients do not fall within the scope of the antimicrobial rulemaking. This amended tentative final monograph applies to products containing antimicrobial ingredients for first aid antiseptic use. As discussed in comment 13, the definitions for skin wound cleanser and skin wound protectant are no longer included in this amended tentative final monograph. The agency will discuss the data submitted by the comment for a product containing no antimicrobial ingredient, but with protective claims, in the rulemaking for OTC skin protectant drug products, in a future issue of the **Federal Register**.

Reference

(1) Comment No. C00107, Docket No. 75N-0183, Dockets Management Branch.

D. Comments on Labeling

15. Several comments contended that FDA does not have the authority to restrict OTC labeling claims to exact wording, to the exclusion of what the comments described as other "equally truthful claims for the products." One comment pointed out that numerous other meaningful and truthful statements will provide useful information and will enhance the safe and effective use of these products. Several comments maintained that manufacturers have a constitutional right to use any truthful, nonmisleading labeling under the first amendment. To support their position, the comments cited *Bigelow* v. *Virginia*, 421 U.S. 809 (1975); *Virginia State Board of Pharmacy* v. *Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748 (1976); *Linmark Associates, Inc.* v. *Willingboro*, 431 U.S. 85 (1977); *Bates* v. *State Bar of Arizona*, 433 U.S. 350 (1977); *Federal Trade Commission* v. *Beneficial Corp.*, 542 F.2d 611, 97 S. Ct. 1679 (1977); and *Warner-Lambert Co.* v. *Federal Trade Commission*, 562 F.2d 749 at 768 (D.C. Cir. 1977).

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 21 CFR 330.1(c)(2), 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 other OTC drug labeling required by a monograph or other regulation (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under the OTC drug monograph or other regulation where exact language has been established and identified by quotation marks, e.g., 21 CFR 201.63 or 330.1(g).

In the previous tentative final monograph, supplemental language relating to indications had been proposed and captioned as "*Other allowable statements*" in §§ 333.90, 333.92, and 333.93. Under FDA's revised labeling policy (51 FR 16258), such statements are included at the tentative final stage as examples of other truthful and nonmisleading language that would be allowed elsewhere in the labeling. In accordance with the revised labeling policy, such statements would not be included in a final monograph.

In preparing this amended tentative final monograph, the agency has reevaluated these "other allowable statements" to determine whether they should be incorporated, wherever possible, as part of the indications developed under the monograph. The "*Other allowable statements*" proposed in the previous tentative final monograph that are covered by this amended tentative final monograph appeared in § 333.90(b)(2) for skin antiseptic, in § 333.92(b)(2) for skin wound cleanser, and in § 333.93(b)(2) for skin wound protectant. The statement "provides a protective physical (and chemical) barrier" proposed for a skin wound protectant has been deleted in this tentative final monograph because it does not fall within the scope of the antimicrobial rulemaking. (See comment 14.) Other previously proposed "*Other allowable statements*" are discussed in comment 16.

16. Two comments suggested that the following labeling claims would be appropriate for first aid antiseptics: "degerms," "kills germs," "kills bacteria," "bactericidal" (if applicable as, for example, for alcohol), "contains antimicrobial ingredients," "microbiocidal," "first aid product," and "reduces the risk of infection." One of the comments argued that the labeling claims "prevents overt infection" or "controls infection" should be permitted if appropriate additional studies are provided.

Other previously proposed "*Other allowable statements,*" i.e., "contains antibacterial ingredient(s)," "contains antimicrobial ingredient(s)," "does not delay wound healing," and "nonirritating" are similar to the claims suggested by the comments, and the agency is evaluating all of these statements concurrently. The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. One aspect of the program is to develop standards for certain parts of the labeling of OTC drug products. FDA has found that it is simply not practical—in terms of time, resources, and other considerations—to set standards for all labeling found on OTC drug products. Accordingly, OTC drug monographs directly address only those labeling items that are related in a significant way to the safe and effective use of covered products by lay persons. These labeling items are the product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

The agency finds that most of the terms suggested by the comments and previously proposed as "*Other allowable statements,*" while descriptive of the action of first aid antiseptic products, do not relate in a significant way to the safe and effective use of these products and, therefore, are outside the scope of the monograph.

However, the OTC drug review is also intended to ensure that OTC drug products are not misbranded. Therefore, the agency evaluates claims made on OTC drug product labels on a product-by-product basis, under section 502 of the act (21 U.S.C. 352), to determine whether those claims are false or misleading. Any claim that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in any portion of the labeling that is required by the monograph. Such a claim also may not detract from the required information. Therefore, the claims requested by the comments or previously proposed as "*Other allowable statements,*" except for those discussed below, may be included on the labeling of first aid antiseptic drug products provided that they are not intermixed with labeling established by the monograph and that they are not false or misleading.

The agency does not believe the average consumer would understand the word "overt" in the phrase "prevents overt infection." As for the phrase "controls infection," the agency believes it may mislead the consumer into assuming the product is intended for use in treating an existing infection. The agency is proposing "helps prevent infection" as a suitable alternative to the two phrases above.

The agency believes that claims such as "degerms," "degerming," "kills germs," "kills bacteria," "bactericidal," and "microbiocidal" could be potentially misleading to the average consumer if directly associated with the term "infection" that is included in the indication because the terms "kill" and "-cidal" may be interpreted to imply elimination of all bacteria on the skin when, in fact, topical antiseptics used on the skin only decrease the number of certain bacteria. However, the agency acknowledges that these terms are familiar to the average consumer and may be useful in describing the product's action or intended effect. Although these terms are not included in the monograph, they may be included in labeling that is not intermixed with monograph labeling as described above.

17. One comment requested that the following phrases (or their equivalent) be added to the monograph: Under proposed § 333.92(b)(1), "to clean and kill germs in superficial wounds," and under proposed § 333.92(b)(2), "contains a safe and effective germ-killing active ingredient." The comment also suggested that the indication "contains antimicrobial ingredient," in proposed § 333.92(b)(2) for skin wound cleansers, be expanded to provide a lay definition of "antimicrobial ingredient" because most consumers would not fully understand the meaning of the statement.

The skin wound cleanser category (proposed § 333.92) is not included in this amended antimicrobial tentative final monograph. As discussed in comment 13, all antimicrobial-containing products to be used on minor cuts, scrapes, and burns are now included in a single category, i.e., first aid antiseptic drug products.

The agency has considered the comment's request to include additional phrases to expand and clarify the meaning of "antimicrobial ingredient." The agency agrees with the comment that labeling should be more informative and has provided several optional statements in § 333.50 of the amended tentative final monograph. However, as discussed in comment 16, the agency believes that a number of terms, e.g., "kills germs," are descriptive but outside the scope of the OTC drug monograph. If such terms are included in labeling, they may not appear in any portion of the labeling required by the monograph and may not detract from such required information.

18. One comment from a manufacturer of a skin wound protectant requested that the claim "protects against * * * diaper rash" be added to the list of indications in proposed § 333.93(b)(1) for skin wound protectants. The comment stated that its product enjoys considerable use in the treatment of diaper rash, but that if an indication for diaper rash is not included in the monograph, the product could not be promoted for one of its primary uses.

As noted in comment 13, the skin wound protectant category is not included in the amended antimicrobial tentative final monograph. In the **Federal Register** of September 7, 1982 (47 FR 39436), the administrative record for skin protectant drug products was reopened to include the recommendations on diaper rash drug products of the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) because that Panel concluded that the use of skin protectants may prevent skin irritation associated with diaper rash (47 FR 39436 at 39439).

In the tentative final monograph for OTC skin protectant diaper rash drug products, the claim "protects * * * diaper rash" was proposed as a monograph claim (June 20, 1990; 55 FR 25204 at 25232). In the tentative final monograph for OTC topical antimicrobial diaper rash drug products, no antimicrobial ingredients were proposed as Category I for the claim "helps protect against skin infection associated with diaper rash" (June 20, 1990; 55 FR 25246 at 25281). Final agency decisions will appear in the final monographs for OTC diaper rash drug products in a future issue of the **Federal Register**.

19. One comment recommended that antimicrobial soaps be allowed to make claims relating to general health care and personal hygiene similar to the claims allowed for health-care personnel handwashes. The comment stated that an antimicrobial soap will reduce bacteria or the transfer of potentially pathogenic organisms in the home, and therefore serves as a preventive health care aid in controlling diseases such as impetigo, pyoderma, and erythrasma. To inform consumers of such benefits, the comment suggested that the "other allowable statements" for antimicrobial soaps be expanded to include some of the labeling for health-care personnel handwashes in proposed § 333.85(b)(1).

The agency will address these uses of such products in a future **Federal Register** notice.

20. One comment objected to that part of the directions for use for skin wound protectants (§ 333.93(d)) that states, "After gentle washing with soap and water, * * *." The comment contended that in certain instances "gentle washing with soap and water" does not constitute acceptable medical practice, and requested that the wording should simply be "apply small amount directly to the affected area." Two comments objected to that part of the directions for use that states "May be applied 1 to 3 times daily." One comment stated that such a limitation of use should be based on the active ingredient(s). The comment recommended the following wording: "Labeling should also contain the recommended time interval (if any) between applications required to provide a protective (physical and chemical) barrier on the skin." The other comment pointed out that first aid products are intended only for single or a few applications. This comment contended that labeling that implies repeated use will be confusing to the consumer and suggested substituting labeling that does not assume repeated use.

The agency believes that first aid of small superficial wounds begins with adequate cleaning of the wound and, therefore, disagrees with the comment's suggestion to delete all references to cleaning the wound. However, because alkaline soap may not be appropriate for use on damaged tissue, the agency proposes to replace the phrase "after gentle washing with soap and water," with the phrase "clean the affected area."

Regarding the directions to use 1 to 3 times daily, such a direction is appropriate for these products, will discourage unlimited and repeated use, and yet will allow for limited applications as needed after a bath or after washing.

Therefore, the agency is proposing the following general directions for use for first aid antiseptics in § 333.50(d): "Clean the affected area. Apply a small amount of this product on the area 1 to 3 times daily. May be covered with a sterile bandage."

21. One comment requested that the portion of the directions for skin wound protectants in proposed § 333.93(d) that states "* * * cover with sterile gauze if desired" be deleted because covering a wound may retard healing in some cases. The comment submitted no data to support its request.

The agency agrees with the comment that it is not always desirable to cover a wound. However, rather than deleting any reference to covering a wound, the agency believes that consumers should be informed if precautions should be taken when covering a wound. For first aid antiseptics that do not require special labeling concerning bandages, the agency is proposing the directions for use stated in comment 20.

22. Objecting to the proposed warning "Do not bandage tightly" (§ 333.92(c)(4)), one comment stated that the warning does not make sense in terms of the way in which quaternary ammonium skin wound cleansers such as benzalkonium chloride are generally used. In place of the proposed warning, the comment recommended more explicit instructions for use, e.g., "Apply and let dry, before bandaging," and submitted data to support its position that occlusion of the wound with a bandage does not interfere with the safety and effectiveness of the drug (Ref. 1).

As discussed by the Panel (39 FR 33103 at 33132), quaternary ammonium compounds can be irritating to the skin, and the degree of irritation is dependent on concentration and/or occlusion. The Panel stated "There is little irritation potential with the use concentration." Nevertheless, the Panel stated that these compounds should not be covered with occlusive bandaging (39 FR 33116) and recommended the following warning: "Use of solution with occlusive dressing is not advisable." In paragraph 57 of the previous tentative final monograph (43 FR 1210 at 1219), the warning against "occlusive dressing" was revised to "Do not bandage tightly," and included in the warning for all skin wound cleansers. Upon further review of this warning, in the context of the newly proposed first aid category, the agency is proposing not to include a general warning statement, but instead to evaluate each individual ingredient to determine if there is a need for such a statement. The agency has reviewed the data on benzalkonium chloride submitted by the comment (Ref. 1) and determined that they show that occlusion of the wound with a bandage did not interfere with healing of the wound. Accordingly, the

agency concludes that the warning "do not bandage tightly," previously proposed in § 333.92(c)(4), is not necessary for this ingredient at the use concentrations provided for in the proposed monograph. Likewise, the alternate warning previously proposed in § 333.99 in the professional labeling section, i.e., "Do not use solution with occlusive dressing," is no longer being included in the tentative final monograph. The agency has also determined that these warning statements are not necessary for the other two quaternary ammonium compounds included in this monograph. Benzethonium chloride has been shown to be not irritating or sensitizing in two studies on children with diaper rash (Refs. 2 and 3). Methylbenzethonium chloride, a derivative of benzethonium chloride, has been used to prevent and treat skin irritations caused by contact with urine, feces, and perspiration, and has low toxicity and local sensitizing properties (Ref. 4).

The agency notes that first aid antiseptics containing quaternary ammonium compounds are usually applied as solutions or sprays, and agrees with the comment that more explicit directions for use relating to bandaging after applying the product would be useful to consumers. The agency is also aware that a number of other first aid antiseptic ingredients are marketed as solutions or sprays. The agency believes it is appropriate to let a solution or spray dry first before covering the area with a sterile bandage. Accordingly, the agency is incorporating this information in the directions section of this tentative final monograph.

References

(1) Unpublished Clinical Wound Healing Studies on Medi-Quik® submitted by Sterling Drug, Inc., Comment No. SUP013, Docket No. 75N–0183, Dockets Management Branch.

(a) Statistical Analysis of Data from Efficacy Study of Medi-Quik® as a Skin Wound Protectant in Humans.

(b) Studies on Medi-Quik® as a Wound Protectant.

(2) Susca, L.A., and B.G. Genting, "Treatment of Diaper Rash," New York State Journal of Medicine, 69:2858–2862, 1960.

(3) Christian, J.R., and F. Gonzalez, "Topical Treatment of Acute and Chronic Diaper Rash with Amino Acid Creme," Clinical Medicine, 80, 1961.

(4) Osol, A., and R. Pratt, "The United States Dispensatory," 27th Ed., J.B. Lippincott Co., Philadelphia, p. 186, 1973.

23. Two comments objected to the warning "This product is not for use on wild or domestic animal bites. If you have an animal bite, consult your physician immediately," that was proposed for skin antiseptics (§ 333.90(c)(2)), skin wound cleansers (§ 333.92(c)(2)), and skin wound protectants (333.93(c)(2)). One comment pointed out that skin antiseptics, skin wound cleansers, and skin wound protectants may be particularly useful for cleansing or for first aid treatment of wounds, including animal bites, when medical treatment is not immediately available.

Acknowledging that consumers should not rely solely on self-medication for animal bites, the comment suggested the following warning: "If you have an animal bite, consult your physician immediately." The other comment recommended deleting the warning for skin antiseptics in proposed § 333.90(c)(2), arguing that it is inappropriate because consumers know they cannot rely solely upon antiseptics to treat animal bites and that they should be examined by a physician. The comment further contended that including this type of warning in the labeling may cause consumers to view other important labeling statements on OTC drug products with skepticism.

The agency agrees that most consumers would know that a severe injury from an animal bite needs medical attention; however, consumers may not be as aware of the dangers of the superficial bites of small animals. Although bites from small wild or domestic animals, such as racoons or cats, may appear to be minor cuts, they can result in skin infections or possibly even in rabies. Consequently, the agency believes that an animal bite warning is necessary on OTC first aid antiseptic drug products to warn consumers against relying on self-medication for any animal bite. However, the agency believes that, rather than having a separate warning for animal bites, it is preferable to add the term "animal bites" to the warning that lists other conditions requiring medical attention. Therefore, the agency is proposing the following revised warning for first aid antiseptic drug products in § 333.50(c)(1) in this tentative final monograph: "In case of deep or puncture wounds, animal bites, or serious burns, consult a doctor."

24. One comment objected to the proposed warnings against the use of skin antiseptics, skin wound cleansers, and skin wound protectants for more than 10 days (§§ 333.90(c)(3), 333.92(c)(3), and 333.93(c)(3)). The comment pointed out that these products are not recommended for daily use and that a warning that implies repeated use will be confusing to consumers. The comment also pointed out a discrepancy between the wording in the second sentence of the warning for skin antiseptics which states: "If the infection worsens or persists, see your physician," and the equivalent warning for skin wound cleansers and skin wound protectants, which states: "If the condition worsens or persists, see your physician." The comment maintained that the warning for skin antiseptics is confusing because it assumes that an infection has occurred when, in fact, none may have occurred, but the wound nevertheless requires medical attention. The comment suggested that all three warnings be replaced by one warning as follows: "If condition does not improve in 10 days, see your physician."

Another comment stated that the warnings in proposed § 333.93 (c)(3) and (c)(5) convey the same message. The warning in § 333.93(c)(3) states, "Do not use this product for more than 10 days. If the conditions worsen or persist, see your physician." The warning in § 333.93(c)(5) states, "If itching, redness, irritation, swelling or pain develops and persists for more than 1 week or increases, it may be a sign of infection or allergy. Discontinue use at once and consult your physician." The comment requested that this warning be deleted.

A third comment requested that alcohol drug products also be labeled with a warning to consult a physician if the condition worsens or persists for more than 1 week.

As noted in comment 13, the three categories formerly identified as skin antiseptic, skin wound protectant, and skin wound cleanser have all been included in the first aid antiseptic category, and all drugs in this category will bear the same warnings.

The agency disagrees that the statement limiting the period of use implies that the product is recommended for repeated daily use. The purpose of a statement limiting use of a product is to alert the consumer to the period of time that is reasonable for self-treatment of a condition and to convey the message that a condition that persists beyond this period should be treated by a doctor.

The agency agrees with the comments that the warnings in § 333.93 (c)(3) and (c)(5) convey the same message and that the statement in § 333.90(c)(3) "If the infection worsens or persists, see your physician" implies an existing infection and may cause confusion about when a physician should be consulted. The proposed warning in § 333.93(c)(5) could confuse consumers because it states that the user should stop using the product if itching, redness, swelling or pain develops or increases. These are the same symptoms that often occur after minor skin injury, the condition for

which topical first aid products are indicated. Therefore, for clarity, §§ 333.90(c)(3), 333.92(c)(3), and 333.93 (c)(3) and (c)(5) have been combined and revised. The proposed warning, redesignated § 333.50(c)(1)(ii), states: "Stop use and consult a doctor if the condition persists or gets worse. Do not use longer than 1 week unless directed by a doctor."

In addition, the agency agrees with the comment that alcohol drug products should also bear such a warning. Although a physician may advise using an OTC topical first aid antiseptic for longer than 1 week, consumers should not self-medicate for a longer period of time without consulting a doctor. The Antimicrobial II Panel, in its advance notice of proposed rulemaking for OTC topical antibiotic drug products (42 FR 17642 at 17653), stated that "most small superficial skin wounds including burns, cuts, and abrasions will heal almost completely within 1 week." That Panel expressed concern that "continued use of a topical antibiotic preparation on an unhealed lesion may delay diagnosis and treatment of a more serious skin disease, e.g., a spreading deep bacterial infection, or a wound contaminated with foreign debris such as glass." (42 FR 17653). Because the situation involving use of first aid antiseptics is the same, the warning proposed in this document specifies 1 week rather than 10 days. A 1-week use limit also is consistent with the agency's warning in the final monograph for OTC topical first aid antibiotic drug products. (See 21 CFR 333.150(c)(2).)

25. One comment objected to the number of warnings required for skin wound protectants in proposed § 333.93 (c)(1) through (c)(7). The comment stated that multiple warnings will discourage self-treatment, confuse consumers, and force them to request professional assistance for minor ailments from an overburdened health care distribution system. The comment added that compliance with such lengthy labeling may be difficult because of lack of label space and suggested that, of the seven warnings, only the following two are essential: "For external use only" and "Do not use this product for more than 10 days. If the conditions worsen or persist, see your physician." The comment recommended deletion of all the other proposed warnings because "it is of no benefit to require the appearance of all possible warnings on the label of an over-the-counter medication."

The agency agrees that some of the warnings could be combined or revised without losing their intent. However, limiting the warnings to only the two suggested by the comment would not provide consumers with adequate information. The agency recognizes that it is not necessary or even possible to identify every improper use of a drug that could occur and to list such information on the drug label. Only those warnings that are necessary for the safe and effective use of the product should be included.

The indication for use in this amended tentative final monograph, "First aid to help prevent infection in minor cuts, scrapes, and burns," and the 1-week use limitation warning (see comment 24) should be sufficient to inform the consumer that first aid antiseptics are not to be used on longstanding skin conditions. Therefore, the warning previously proposed in § 333.93(c)(7), "Do not use on chronic skin conditions such as leg ulcers, diaper rash, or hand eczema," is not being included in this amended tentative final monograph.

In addition, the agency has combined and revised the proposed warnings in § 333.93 (c)(3) and (c)(5). (See comment 23.) The proposed warnings in § 333.93 (c)(2) and (c)(4) have also been combined. (See comment 24.) The proposed warning in § 333.93(c)(1) has been retained as suggested by the comment. The proposed warning in § 333.93(c)(6), "Do not use in the eyes," has been expanded to include "or apply over large areas of the body." This revision is in keeping with the agency-initiated change described in the tentative final monograph for OTC first aid antibiotic drug products (see 47 FR 29986 at 29998) that was finalized in the final monograph for those drug products (see 52 FR 47312 at 47324 and 21 CFR 333.50(c)(1)).

The agency believes that these changes will result in labeling that is clear to consumers and that assures safe and proper use of first aid antiseptic drug products.

26. Several comments objected to the warning for antimicrobial bar soaps in proposed § 333.80(c), "Do not use this product on infants under 6 months of age." Some comments recommended deleting the warning and submitted data to show that antimicrobial soaps containing triclosan and triclocarban are safe for use on infants (Ref. 1). Three comments argued that, contrary to the agency's conclusions at 43 FR 1213 and 1232, the data on the use of triclosan in monkey neonates should be regarded as adequate to show that triclosan is safe for human infant use (Ref. 2). The comments further argued that the warning in proposed § 333.80(c) is misleading and will have an unfavorable commercial impact because it will lead consumers to believe that antimicrobial soaps are harmful to users of all ages and therefore consumers will not purchase them. One comment requested that the warning not be required for soap bars weighing 2.5 ounces or less because of the limited space on the label for printing the warning and because these bars probably would not be used on infants over a long period of time.

The labeling section (333.70) in the advance notice of proposed rulemaking (39 FR 33103 at 33141) and the labeling section (333.80) in the tentative final monograph (43 FR 1210 at 1247) entitled "Antimicrobial soap" were intended to apply to antimicrobial bar soaps customarily used in the home. The Panel and the agency recognized that these products were primarily used to "reduce odor" and as "deodorant soaps." No directions for use were proposed in the tentative final monograph because of the known and customary conditions of use. As stated in comment 10, soaps containing antimicrobial ingredients and making only deodorant claims are considered cosmetics and thus are not being included in this amended tentative final monograph. (The regulations governing cosmetics are located in 21 CFR parts 700 to 740.) If the agency determines that cosmetic soap products containing an antimicrobial ingredient need a warning concerning use on infants under 6 months of age, the agency will propose to amend the cosmetic regulations accordingly.

This amended tentative final monograph does not include any products labeled for total body or chronic use in infants. Therefore, the labeling previously proposed in § 333.80, including the warning in § 333.80(c), is not being included in this tentative final monograph.

References

(1) Comment Nos. C00061, CP0002, SUP015, SUP018, C00099, C00109, C00115, and C00134, Docket No. 75N–0183, Dockets Management Branch.

(2) Unpublished Nonclinical Safety Data on Metabolism of Triclosan by Newborn Rhesus Monkeys, Submitted by Ciba-Geigy Corp., Comment No. C00109, Docket No. 75N–0183, Dockets Management Branch.

(3) Published and Unpublished Nonclinical Safety Data on Metabolism of Triclocarban by Infants, Submitted by Armour-Dial, Inc., Comment No. LET047, Docket No. 75N–0183, Dockets Management Branch.

E. Comments on Alcohols

27. Two comments stated that the statement of identity for alcohol drug products proposed by the Miscellaneous External Panel in § 333.98(a), "alcohol for topical antimicrobial use," would be

confusing to consumers. One comment contended that the word "topical" is not generally understood to mean pertaining to the surface, much less to be understood to relate to skin treatment. The comment added that the word "alcohol" in the statement of identity is superfluous because alcohol is already required under section 502(e) of the act (21 U.S.C. 352(e)) to be listed on the label as the active ingredient. The comment pointed out that "antiseptic for the skin" has been the statement of identity for a particular alcohol product since 1923 and that this statement of identity is meaningful to the layman in accordance with 21 CFR 201.61. The comment stated that alcohol and isopropyl alcohol products fit the definition of a skin antiseptic in § 333.3(f) and requested that the indications and directions for use for skin antiseptics in § 333.90 (b) and (d) be used for such alcohol and isopropyl alcohol products.

The other comment argued that the Panel's recommended statement of identity was unnecessary and should be deleted because other sections of the topical antimicrobial monograph already specify that antimicrobial-containing drug products (which would include alcohol and isopropyl alcohol) are to be labeled as skin wound cleansers, antiseptics, etc.

The agency is proposing to include alcohol and isopropyl alcohol in the list of antiseptic active ingredients in § 333.10 of this amended tentative final monograph with the statement of identity "first aid antiseptic." The Miscellaneous External Panel's definition of alcohols in § 333.3(k) is not being proposed in this amended tentative final monograph. Thus "topical," "skin," and "alcohol" are not needed as part of the statement of identity. (See comments 9 and 13.) However, the agency has no objection to these words appearing elsewhere in the labeling of these products as additional information to the consumer, provided they do not appear in any portion of the labeling required by the monograph and do not detract from such required information. (See comment 15.) The indications and directions for "first aid antiseptics" are discussed in comments 16, 17, 20, and 21.

28. One comment argued that the Panel's recommended monograph for alcohol drug products is in conflict with the regulations of the Treasury Department's Bureau of Alcohol, Tobacco and Firearms (BATF) pertaining to ethyl alcohol in 27 CFR parts 211 and 212. (27 CFR parts 211 and 212 were removed in the Federal Register of June 2, 1983 (48 FR 24673). Denatured alcohol is now covered in 27 CFR parts 20 and 21.) Under the BATF regulations, denatured ethyl alcohol products containing 70 percent ethyl alcohol are required to be labeled as "Rubbing Alcohol," but under the recommended monograph the identical product could only be labeled as "Alcohol for topical antimicrobial use." The comment pointed out that the Panel itself recognized the effectiveness of alcohol for rubbing uses as well as the fact that these uses had been addressed by another regulatory agency. The comment stated that inconsistency between two regulatory agencies is not sound government policy, is economically unfeasible for manufacturers, and is confusing to consumers. The comment requested that a product that meets the requirements of 27 CFR parts 211 and 212 as well as the requirements of the monograph be allowed to be labeled as a topical antimicrobial product with rubbing indications.

The agency agrees that alcohol drug products for topical antimicrobial use can be labeled, at the option of the manufacturer, to meet both FDA's and BATF's regulations. The appropriate labeling for such a product would include the brand name of the product, if any, and the words "Rubbing Alcohol," in accordance with 27 CFR 211.188 (currently 27 CFR 20.134(e)). This regulation also provides that the manufacturer may include additional statements in the labeling. Thus, the labeling could also contain the words "first aid antiseptic," in accordance with 21 CFR 201.61(b) and proposed § 333.50(a). (See comment 27 for a discussion of "first aid antiseptic" as the statement of identity for these alcohol products.) With this labeling and the labeling proposed in the other parts of § 333.50, a product would meet the requirements of both regulations and provide fully informative labeling to consumers without burdening manufacturers.

29. Noting statements made by the Miscellaneous External Panel (47 FR 22324 at 22327), one comment stated that it appears logical that both alcohol and isopropyl alcohol products should include in their labeling statements to the effect that they "remove dirt and grime" and "do not stain the skin," and that alcohol products should be labeled to "clean and cool the skin" or work "as astringents, counterirritants, or rubefacients." The comment argued that these statements, based on the Panel's report, acknowledge that alcohol products have both cosmetic and medicinal uses and reflect the fact that products with both uses were submitted to the Panel for review.

The agency agrees with the Panel's statements at 47 FR 22327 that alcohols have a variety of uses such as cleaning and cooling the skin. However, these uses are not considered drug uses and as such are not appropriate for inclusion in an OTC drug monograph.

As discussed in comment 16, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. The statement "does not stain the skin" is not significantly related to the safe and effective use of the product. It is thus outside the scope of the rulemaking, as are statements such as "cleaning and cooling" or "remove dirt and grime." Such statements will be evaluated by the agency on a product-by-product basis, under the provisions of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Moreover, any statement that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, terms outside the scope of the monograph may be included elsewhere in the labeling, provided they are not false or misleading.

Because this document addresses only first aid antiseptics, the therapeutic use of alcohol and isopropyl alcohol "as astringents, counterirritants, or rubefacients" will be considered in other rulemakings for external analgesic drug products and skin protectant drug products in future issues of the Federal Register. Alcohol and isopropyl alcohol were classified as Category II by the Miscellaneous External Panel in its statement on OTC astringent drug products, published in the Federal Register of September 7, 1982 (47 FR 39412 at 39425 and 39436 at 39444). The agency concurred with this classification in the tentative final monograph for OTC astringent drug products, published in the Federal Register on April 13, 1989 (54 FR 13490 at 13496).

30. One comment requested the addition of a fourth indication for alcohol active ingredients in proposed § 333.98(b) to allow use as an antibacterial handwash to avoid cross-contamination from one individual to another. The comment argued that products containing alcohols are often used as handwashes by athletic trainers to help prevent the spread of skin

infections from one individual to another in situations in which soap and water are not available, e.g., on the playing field.

Because the scope of this document is limited to first aid products, the indication requested by the comment will not be discussed here. It will be addressed in a future issue of the **Federal Register** covering antimicrobial drug products that are used as antiseptic handwashes.

31. One comment stated that the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (Dental Panel) allowed benzocaine or phenol in 70 percent ethyl alcohol for use on the gums (47 FR 22712 at 22737 and 22740). Therefore, it was inconsistent for the Miscellaneous External Panel to place the statement "For application to mucous membranes" in Category II for alcohol drug products (47 FR 22324 at 22332). The comment pointed out that the Miscellaneous External Panel recommended caution in the use of alcohols on mucous membranes in concentrations recommended for antimicrobial use (60 to 95 percent for ethyl alcohol) (47 FR 22327), but the comment did not believe that this caution necessitated an all-inclusive Category II labeling statement. The comment requested that the phrase "except in products containing specific label directions for such use" be added to make the Category II statement read, " 'For application' to mucous membranes, (except in products containing specific label directions for such use)."

An ingredient or drug product can have multiple uses and thus be reviewed by several different panels. The Dental Panel recommended that ethyl alcohol be permitted as a vehicle in concentrations up to 70 percent in products used on the teeth and gums (47 FR 22737 and 22740), but deferred the review of alcohol as an active antiseptic ingredient in the mouth and throat to the Oral Cavity Panel (47 FR 22715). The Oral Cavity Panel placed alcohol in Category III for antimicrobial use in the mouth, but stated that it was ineffective as an antimicrobial agent at concentrations less than 70 percent and that concentrations higher than 35 percent cause burning of mucous membranes (47 FR 22760 at 22872). The Miscellaneous External Panel evaluated ethyl alcohol for use as a topical antimicrobial agent on the skin. The Panel was concerned that alcohol would be irritating to mucous membranes, recommended caution in this use, and placed the statement "For use on mucous membranes" in Category II.

The indications for alcohol drug products covered by this rulemaking apply only to topical antimicrobial uses on the skin and do not include use on mucous membranes, as in the mouth. The agency will address the use of alcohol as an active ingredient on the mucous membranes of the mouth and throat in the proposed rulemaking for oral health care drug products, to be published in a future issue of the **Federal Register**. In developing its proposals in that document, the agency will consider the recommendations of the three Panels, including appropriate concentrations of alcohol in OTC drug products intended for oral use.

32. Two comments requested that small-volume, single-use products containing alcohol active ingredients be exempted from the warning, "Flammable, keep away from fire or flame." The warning was recommended by the Miscellaneous External Panel in § 333.98(c)(1)(ii) (47 FR 22324 at 22330 and 22333). One of the comments argued that swabs saturated with isopropyl alcohol contain such a minute volume of alcohol, 2.5 to 7 mL in each packet, that the warning about flammability is unnecessary for the protection of consumers and may cause undue alarm. The comment pointed out that the United States Department of Transportation excludes such products from the Hazardous Materials Regulations pertaining to flammable liquids.

This comment also requested that the Miscellaneous External Panel's recommended warning in § 333.98(c)(2) for products containing isopropyl alcohol, "Use only in a well-ventilated area; fumes may be toxic," should not be required for single-use alcohol swab products. The comment stated that this warning was proposed by the Panel based on a case in which a large volume of isopropyl alcohol was used in a poorly ventilated room. The comment argued that a large quantity of swabs saturated with isopropyl alcohol would have to be used for this type of application and this is virtually impossible.

The agency disagrees with the comments that small-volume packages containing alcohol active ingredients should be exempted from the flammability warning. The Department of Transportation finding applies only to the shipping of such products in intact packages, whereas the proposed warning informs consumers of proper use after opening the package. The warning is not intended to alarm consumers, but to caution them against improper use of the ingredients. Even small volumes of alcohol should be kept away from fire or flame. The United States Pharmacopeia (U.S.P.) states that isopropyl rubbing alcohol and rubbing alcohol should be labeled to indicate that they are flammable and are to be stored remote from heat (Ref. 1).

However, the agency agrees with the comment that the warning against use in poorly ventilated areas is not needed on small-volume products containing isopropyl alcohol. In fact, the agency tentatively concludes that such a warning is not needed for any product containing isopropyl alcohol because the labeling in this monograph limits its use, i.e., "do not * * * apply over large areas of the body." The agency has reviewed the adverse reactions upon which the Panel based its warning. The three reported cases of adverse effects (Refs. 2, 3, and 4), apparently due to inhalation of isopropyl alcohol, concerned infants in prolonged contact with isopropyl alcohol. The infants were either wrapped in towels saturated with isopropyl alcohol or the alcohol was applied in tepid sponging. The infants were found unconscious or in a stupor after 4 to 8 hours of contact with isopropyl alcohol. Complete recovery occurred on the day following the incident. These three cases, reported between 1953 and 1969, appear to be isolated, infrequent incidents. A warning similar to the one recommended by the Miscellaneous External Panel most probably would not have prevented the adverse reactions reported.

The agency is not proposing that isopropyl alcohol include a warning for toxic fumes in view of the indications provided for in this document, namely, "First aid to help prevent the risk of skin infection in minor cuts, scrapes, and burns." The agency believes that this indication makes it unlikely that anyone using the product as indicated would be exposed to alcoholic fumes for any extended time. Comments are invited on the need for such a warning, including any reports of adverse reactions due to inhalation that have not yet been brought to the agency's attention.

References

(1) "United States Pharmacopeia XXII—National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 731, 1989.

(2) Garrison, R.F., "Acute Poisoning from Use of Isopropyl Alcohol in Tepid Sponging," Journal of the American Medical Association, 152:317–318, 1953.

(3) Senz, E.H., and D.L. Goldfarb, "Coma in a Child Following Use of Isopropyl Alcohol in Sponging," Journal of Pediatrics, 53:322–323, 1958.

(4) McFadden, S.W., and J.E. Haddow, "Coma Produced by Topical Application of Isopropanol," Pediatrics, 43:622–623, 1969.

33. One comment requested that the concentration range for ethyl alcohol in proposed § 333.55 (47 FR 22324 at 22332) be broadened to include 48 percent (by volume) aqueous ethyl alcohol for the indications recommended by the Miscellaneous External Panel in § 333.98(b) (47 FR 22330 and 22332). The comment argued that a skin antiseptic does not have to be microbiocidal against all microorganisms, but only against those known to cause infection in minor cuts, scratches, and abrasions.

The comment submitted data on the microbiocidal activity of 48 percent alcohol by volume in aqueous solution and of a marketed product containing the same concentration of alcohol against a variety of micro-organisms, including *Staphylococcus aureus* (*S. aureus*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Bacillus subtilis* (*B. subtilus*), Proteus species, and *Candida albicans* (*C. albicans*) (Ref. 1). The comment stated that the minimum inhibitory and minimum biocidal activities of the alcohol solution were effective at fourfold and eightfold dilutions and the minimum inhibitory and minimum biocidal activities of the product were effective at eightfold to sixteenfold dilutions, thus indicating effectiveness even if diluted by body fluids at the wound site.

The comment pointed out that, according to the Miscellaneous External Panel, the potential of alcohol to irritate the skin increases with increasing concentration. The comment concluded that an alcohol product should have a high enough concentration to be effective as a skin antiseptic, yet be mild enough to cause minimal skin irritation.

The agency has reviewed the submitted data, which included studies to measure the minimum in vitro contact time for 48 percent alcohol to kill test micro-organisms. Cultures of test micro-organisms were mixed with the test solution containing 48 percent alcohol and subcultured at the following times: 0 (immediately after mixing), 1, 3, 5, 10, and 15 minutes. The test solution killed many test micro-organisms immediately upon contact and all micro-organisms except *B. subtilis* within 1 minute of contact time. The slight increase in time required for 48 percent alcohol to act was insignificant in terms of effectiveness.

Based on these studies and on the advance notice of proposed rulemaking for alcohol drug products (47 FR 22324), the agency proposes that 48 to 95 percent alcohol be classified as Category I. Any authorized formulation of specially denatured alcohol identified in 27 CFR Part 20 may be used. Although the 48-percent alcohol results in an increased time-to-death compared with 60 percent alcohol, the agency believes that the increase in time-to-death is not significant in products for limited first aid antiseptic use.

The agency recognizes that because of its solvent activity, alcohol is frequently used as a vehicle for first aid antiseptic ingredients as well as many other topical medications. As pointed out by the Miscellaneous External Panel (47 FR 22324 at 22327), alcohol is also capable of altering the stratum corneum (skin surface) and enhancing its permeability, thus facilitating the penetration through the skin of any ingredient that is dissolved in it (Ref. 2). For example, enhanced penetration has been demonstrated for iodine (Ref. 3). It is recognized that a wide range of ethyl alcohol concentrations have antiseptic properties (47 FR 22328). However, based upon submitted data for marketed products, only ethyl alcohol in a concentration range of 48 to 95 percent is considered to be an active concentration range for first aid antiseptic use.

The agency notes that the Miscellaneous External Panel included three indications for ethyl alcohol in § 333.98(b): (1) "For first aid use to decrease germs in minor cuts and scrapes," (2) "To decrease germs on the skin prior to removing a splinter or other foreign object," and (3) "For preparation of the skin prior to an injection." Because the agency is now proposing a new first aid antiseptic category for many ingredients, including alcohol, and a general indication, e.g., "First aid to help prevent infection in minor cuts, scrapes, and burns," the agency has not adopted the Panel's first indication. Describing the intent of a product, i.e., "help prevent infection," is more appropriate in a general indication to be included in the monograph than stating a mode of action, i.e., "decreases germs."

The agency believes that the second indication, "to decrease germs on the skin prior to removing a splinter or other foreign object," is a descriptive statement giving an example of a particular kind of first aid. Such illustrative statements are outside the scope of the monograph. Such statements will be evaluated by the agency on a product-by-product basis, under the provision of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Moreover, any statement that is outside the scope of the monograph, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, terms outside the scope of the monograph may be included elsewhere in the labeling, provided they are not false or misleading.

The third indication, "For preparation of the skin prior to an injection," will be discussed in a future **Federal Register** publication on non-first aid uses of antimicrobial ingredients.

References

(1) Comment No. C00142, Docket No. 75N–0183, Dockets Management Branch.

(2) Scheuplein, R. J., and I. H. Blank, "Mechanism of Percutaneous Absorption. IV. Penetration of Nonelectrolytes (Alcohols) from Aqueous Solutions and from Pure Liquids," Journal of Investigative Dermatology. 60:286–296, 1973.

(3) Reeve, T. S., G. A. E. Coupland, and I. B. Hales, "The Effect on Serum Iodine Levels of Painting Tincture of Iodine on the Skin," Medical Journal of Australia, 1: 891–892, 1973.

F. Comments on Chlorhexidine Gluconate

34. Several comments requested that the agency include chlorhexidine gluconate as a Category I ingredient in any amended tentative final monograph. The comments submitted references and data to establish general recognition of safety and effectiveness (Ref. 1) and stated that chlorhexidine gluconate solution is recognized in the "British Pharmacopeia" (Ref. 2) and is formulated in a wide range of products that have been successfully marketed to a material extent and for a material length of time in other countries. The comments asserted that when formulated in compliance with FDA's current good manufacturing practice regulations (21 CFR Part 211), chlorhexidine products are safe and effective for use as skin wound cleansers, skin wound protectants, patient preoperative skin preparations, skin antiseptics, surgical hand scrubs, and health-care personnel handwashes.

A reply comment argued that chlorhexidine gluconate, currently marketed in the United States under approved NDA's, is not eligible for an OTC drug monograph because the ingredient has not been marketed within this country to a material extent and for a material length of time. The comment added that variations in final formulations may alter the safety and effectiveness of the ingredient. The comment submitted data (Ref. 3) to support this viewpoint and requested that chlorhexidine gluconate be classified in Category II.

In the previous tentative final monograph (43 FR 1210), chlorhexidine gluconate (4 percent solution) was neither addressed nor categorized as Category I, II, or III. However, subsequent to the tentative final monograph, the agency granted a petition (Ref. 4) and in the **Federal Register** of March 9, 1979, reopened the administrative record to allow interested persons an opportunity to submit data and information (44 FR 13041). The comments (Ref. 1) and reply comment (Ref. 2) were submitted in response to that notice. However, since that time a majority of the comments on chlorhexidine submitted in response to the notice have been withdrawn (Ref. 5). While the data and information remain on public display as part of the administrative record, they are no longer being considered in this rulemaking.

The agency has reviewed the marketing history of chlorhexidine gluconate and finds that although it has been marketed for professional or hospital use, this ingredient has never been marketed in the United States for any first aid use. Accordingly, chlorhexidine gluconate 4 percent aqueous solution as a first aid antiseptic is a new drug and is not included in this proposed monograph.

The professional uses for chlorhexidine gluconate requested by the comments (Ref. 1), i.e., surgical hand scrub and health-care personnel handwash, will be addressed separately in the segment of this rulemaking dealing with uses other than first aid in a future issue of the **Federal Register.**

References

(1) Comment Nos. C00110, C00116, C00120, C00130, C00131, C00136, C00137, EXT018, RC0002, RC0005, CP0003, LET012, LET014, LET016, SUP030, SUP033, SUP038, and SUP040, Docket No. 75N–0183, Dockets Management Branch.

(2) "British Pharmacopeia," Vol. I, Her Majesty's Stationery Office, London, pp. 100–101, 1960.

(3) Comments No. RC001 and RC004, Docket No. 75N–0183, Dockets Management Branch.

(4) Citizen Petition No. CP003, Docket No. 75N–0183, Dockets Management Branch.

(5) Comments No. WDL003, WDL004, and WDL005, Docket No. 75N–0183, Dockets Management Branch.

G. Comments on Chloroxylenol

35. A number of comments disagreed with the agency's Category III classification of chloroxylenol in the tentative final monograph. They argued that reevaluation of the data previously submitted to the agency along with new data that have been submitted (Refs. 1 through 16) would provide adequate justification for classifying chloroxylenol in Category I for safety and effectiveness for use in antimicrobial soaps, health-care personnel handwashes, patient preoperative skin preparations, skin antiseptics, skin wound cleansers, skin wound protectants, and surgical hand scrubs. Several comments pointed out that the Antimicrobial II Panel unanimously concluded that chloroxylenol is generally recognized as safe for topical use in athlete's foot and jock-itch preparations. One comment stated that the Panel placed hexylresorcinol in Category I and chloroxylenol in Category III as a skin wound cleanser, but that a comparison of the available data clearly indicates that the safety data available on chloroxylenol are superior to those for hexylresorcinol.

Data submitted by the comments regarding safety and effectiveness for uses other than first aid, e.g., health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub will be discussed in the segment of this rulemaking dealing with uses other than first aid in a future issue of the **Federal Register.**

In the tentative final monograph, chloroxylenol was categorized as Category III for safety and effectiveness as a skin antiseptic, skin wound cleanser, and skin wound protectant, and it was recommended that effectiveness testing, both in vitro and in vivo, be done (43 1210 at FR 1238). The agency also requested data to show the effects of chloroxylenol on wound healing (43 FR 1238).

Subsequent to the tentative final monograph, the Antimicrobial II Panel in the advance notice of proposed rulemaking for OTC topical antifungal drug products categorized chloroxylenol (0.5 to 3.75 percent) as safe (Category I) for short-term use (up to 13 weeks) (47 FR 2480 at 12535).

The agency has reviewed the data, which include wound-healing studies, submitted by the comments. Bradbury and Hayden (Refs. 9 and 10) described studies on the effect of various concentrations of chloroxylenol up to 4.8 percent, on wound healing in rats. Wound healing was assessed by measuring wound tensile strength and histopathology. The results showed that none of the treatments significantly altered wound tensile strength or caused a significant delay in the healing process.

Maibach (Refs. 11 and 22) described two clinical studies that used the forearms of human volunteers to assess the effects of petroleum jelly and carbolated petroleum jelly, containing chloroxylenol 0.5 percent, on wound healing. In one study (Ref. 11), the forearm skin was stripped and treated twice daily for 5 days. In the other study, incisions were made in the forearm and treated three times in 24 hours (Ref. 12). There were no differences in the rates of wound healing between control sites and treated sites.

These studies (Refs. 9 through 12) showed that chloroxylenol 0.5 percent to 4.8 percent did not delay wound healing and affirm the Antimicrobial II Panel's conclusion that chloroxylenol is safe for short-term use. Accordingly, the agency is reclassifying chloroxylenol to Category I for safety for use as a first aid antiseptic.

The in vitro data demonstrate that formulated chloroxylenol, in the presence of 5 percent serum (37 °C) is effective within 5 to 10 minutes. The in vivo data, derived from studies of artificial contaminants on the skin of human test subjects, showed that chloroxylenol-containing product reduced the number of staphylocci, pseudomonas, escherichia, and streptococci by greater than one log (i.e., 1 $\log_{10}$) within 5 minutes. However, none of the studies demonstrate the contribution of chloroxylenol to the formulated product.

The agency does not consider the data regarding the antiseptic activity of chloroxylenol itself to be adequate. While the data are considered sufficient to support in vitro and in vivo effectiveness for the finished products (Refs. 13 through 16), the available data are inadequate to show the contribution of the chloroxylenol. Because these finished products contain several additional ingredients, i.e., surfactants, isopropanol, pine oil, or ethylenediaminete-tracetic acid (EDTA), any of which could have contributed germicidal activity, conclusions regarding chloroxylenol's active contribution to the products' efficacy cannot be supported. Accordingly, in this proposed rule chloroxylenol is being proposed as a Category III first aid antiseptic ingredient for effectiveness.

References

(1) Unpublished Clinical Safety and Effectiveness Studies on Aqueous Soap Formulations, submitted by the Pennwalt Corp., Comment No. 0B0007, Docket No. 75N–0183, Dockets Management Branch.

(a) Controlled Clinical Study Comparing the Activity of Fresh, Camay Soap, and Phisohex Against the Natural Bacterial Flora of the Hand.

(b) Antimicrobial Activity of PCMX, Triclosan, and TCC.

(c) Repeated Insult Patch Testing of Fresh Soap.

(2) Unpublished Nonclinical and Clinical Studies, and Protocols, submitted by the

Pennwalt Corp., Comment No. C00096, Docket No. 75N–0183, Dockets Management Branch.

(a) Part I: PCMX Toxicosis, final reports of completed studies, interim reports of incomplete studies, and Preclinical Testing Protocol.

(b) Part II: Complete Reports on Clinical Safety and Efficacy and In Vitro Efficacy Studies.

(3) Unpublished Clinical Effectiveness Studies on Aqueous Soap Formulations, submitted by Chemical Specialties, Inc., Comment No. C00122, Docket No. 75N–0183, Dockets Management Branch.

(a) Protocol and Results of a Glove Juice Hand Washing Test Performed with PHLO Antimicrobial Skin Cleanser.

(b) Results of a Zone of Inhibition and Assay Performed on Aged Samples of PHLO Antimicrobial Skin Cleanser.

(4) Unpublished Clinical Safety and Effectiveness Studies on Aqueous Soap Formulations, submitted by Sani-Fresh, Comment No. C00123, Docket No. 75N–0183, Dockets Management Branch.

(a) Bactericidal Activity of Envair Antiseptic Hand Soap.

(b) Dermal Irritation Study.

(c) Insult Patch Test.

(d) Bacterial Kill Test.

(e) Hand-wash Effectiveness Test.

(5) Unpublished In Vitro Effectiveness Studies Performed on Aqueous Soap Solutions, submitted by Seagull Chemical, Comment No. C00125, Docket No. 75N–0183, Dockets Management Branch.

(a) AOAC Available Chlorine Germicidal Equivalent Concentration Test.

(b) The Antimicrobial Activity of a Sample.

(6) Published and Unpublished Nonclinical and Clinical Safety Studies, submitted by Ferro Corp., Comment No. SUP011, Docket No. 75N–0183, Dockets Management Branch.

(7) Published and Unpublished Safety and Effectiveness Studies, submitted by Scientific and Regulatory Services, Comment No. SUP012, Docket No. 75N–0183, Dockets Management Branch.

(8) Unpublished Clinical Safety and Effectiveness Studies, submitted by Chesebrough Ponds, Inc., Comment No. SUP010, Docket No. 75N–0183, Dockets Management Branch.

(a) The Effects of Vaseline Petroleum Jelly and Vaseline First Aid Carbolated Petroleum Jelly on Epidermal Wound Healing—A Controlled Clinical Laboratory Study, April 29, 1976.

(b) The Effect of Vaseline Petroleum Jelly and Vaseline First Aid Carbolated Petroleum Jelly on Healing of Experimental Skin Wounds, January 13, 1977.

(9) Bradbury, S.J., and J. Hayden, "Effect of Dettol® on Wound Healing in Rats," Report No. RC 76132, unpublished study, Comment No. SUP05, Docket No. 75N–0183, Dockets Management Branch.

(10) Bradbury, S.J., and E.J. Hayden, "Dettol® Wound Healing," unpublished study, Project No. RC 1081, 1978, Comment No. SUP012, Docket No. 75N–0183, Dockets Management Branch.

(11) Maibach, H.I., "The Effects of Vaseline® Petroleum Jelly and Vaselines First Aid Carbolated Petroleum Jelly on Epidermal Wound Healing—A Controlled Clinical Laboratory Study," unpublished study, Comment No. SUP010, Docket No. 75N–0183, Dockets Management Branch.

(12) Maibach, H.I., "The Effect of Vaseline® Petroleum Jelly and Vaseline®First Aid Carbolated Petroleum Jelly on Healing of Experimental Skin Wounds," unpublished study, Comment No. SUP010, Docket No. 75N–0183, Dockets Management Branch.

(13) Munton, T.J., and J. Prince, "The Bacteriostatic and Bactericidal Activity of Dettol® Against a Range of Recently Isolated Mesophilic Strains Including Members of the Normal Flora and Cutaneous Pathogens of the Skin," unpublished study, No. BL 75/4, 1975, Comment No. SUP003, Docket No. 75N–0183, Dockets Management Branch.

(14) Prince, J., and K.A. Barker, "A Comparison of the In-Vitro Activity of Dettol®, Hexylresorcinol and Benzalkonium Chloride," unpublished study, No. BL 76/28, 1976, Comment No. SUP003, Docket No. 75N–0183, Dockets Management Branch.

(15) Munton, T.J., and J. Prince, "The Bactericidal Activity of Dettol® on Skin Artificially Contaminated with Micro-organisms Using the Replica Plating Technique," unpublished study, No. BL 75/14, RC 7565, 1975, Comment No. SUP003, Docket No. 75N–0183, Dockets Management Branch.

(16) "Scientific Information on the 'In-vitro' and 'In-vivo' Antimicrobial Activity of Dettol® as Determined in the Bacteriological Laboratories of Reckitt and Colman, Hull," published report, Comment No. C00062, Docket No. 75N–0183, Dockets Management Branch.

H. Comments on Hydrogen Peroxide

36. Two comments requested that hydrogen peroxide solution (3 percent) be included in the monograph as a Category I skin antiseptic. One comment pointed out that no mention of the ingredient is made in the proposed or tentative final monograph even though hydrogen peroxide has been recognized by the U.S.P. for many decades as a topical anti-infective for application to skin and mucous membranes. The comment submitted two references to show that hydrogen peroxide is a desirable skin antiseptic that can be used safely and effectively by the layman (Refs. 1 and 2).

Hydrogen peroxide solution (3 percent) for use as a skin antiseptic was not classified in the previous tentative final monograph because it was deferred to the Miscellaneous External Panel. (See comment 85, 43 FR 1210 at 1223.) A manufacturer had made a submission (Ref. 3) on hydrogen peroxide (U.S.P., 3 percent) as a first aid antiseptic drug product to the Miscellaneous External Panel but that Panel disbanded before it reviewed hydrogen peroxide. The agency subsequently concluded that it would be appropriate to categorize hydrogen peroxide as a first aid antiseptic in this antimicrobial rulemaking. Accordingly, the agency requested and received permission from the manufacturer to place the manufacturer's submission (Ref. 3) on public display in the Dockets Management Branch under the antimicrobial docket number (Ref. 4).

The submission forwarded by the manufacturer (Ref. 3) included labeling for a currently marketed product containing hydrogen peroxide solution U.S.P. 3 percent, which states: "First aid antiseptic" "For treatment of minor cuts and abrasions." The submission also included safety and effectiveness data from published articles and unpublished studies. These data indicate that hydrogen peroxide inhibits *S. aureus, Salmonella typhosa, Escherichia coli (E. coli), Proteus vulgaris, Klebsiella pneumoniae, Streptococcus hemolyticus,* and *P. aeruginosa.* The manufacturer also provided in vitro data to show that 3 percent hydrogen peroxide reduced the number of *S. aureus* ATCC 6538P by 3 logs (3 $\log_{10}$) within 5 minutes and completely inhibited all bacteria within 10 minutes.

In a separate OTC drug rulemaking, for OTC oral mucosal injury drug products, the agency found hydrogen peroxide (3 percent in aqueous solution) safe for short-term use up to 7 days. (See the **Federal Register** of July 26, 1983, 48 FR 33984 at 33993.)

Hydrogen peroxide achieves its intended benefit in vivo by means of both a mechanical action and a measurable antibacterial action. Because hydrogen peroxide has been demonstrated to be both safe and effective for use in minor wounds, the agency is proposing to classify hydrogen peroxide (3 percent in aqueous solution) as Category I for use as a first aid antiseptic drug product.

References

(1) "Antiseptics and Disinfectants," *in* "AMA Drug Evaluations," 2d Ed., American Medical Association, Publishing Sciences Groups, Inc., Ashton, MA, p. 653, 1973.

(2) Schumb, W. C., C. N. Satterfield, and R. L. Wentworth, "Hydrogen Peroxide," American Chemical Society Monograph Series, 128, Reinhold Publishing Corp., New York, 1955.

(3) OTC Volume 160031.

(4) Letter from M. Kaplan, Parke-Davis, Division of Warner Lambert and Co., to W. E. Gilbertson, FDA, dated July 12, 1982, Comment No. LET051, Authorizing Public Display of OTC Volume No. 160031, Docket No. 75N–0183, Dockets Management Branch.

I. Comments on Iodine and Iodophors

37. One comment objected to the classification of iodine tincture in Category III for use as a skin antiseptic. To justify Category I status, the comment cited the more than 130-year

history of use of iodine tincture as a household first aid product and the extensive literature on iodine as an antiseptic published during the past several decades. The comment submitted two studies to support its position (Refs. 1 and 2). According to the comment, the study by Salle and Catlin (Ref. 1) showed that iodine tincture (2 percent) has the highest germicidal activity and the lowest toxicity of the germicides tested. The comment pointed out that the publication by Gershenfeld and Witlin (Ref. 2) concluded that iodine was a highly effective bactericidal agent against many different species of microorganisms at high dilution and within a wide pH range; and that it possessed a very low toxicity to tissues as determined by many varied in vitro and in vivo toxicity tests, including tests on human skin. The comment added that an extensive list of additional references has been included as part of the cited studies, and that these references should help resolve the questions raised by the Commissioner. The comment recommended that iodine tincture be placed in Category I.

In the tentative final monograph, the agency concluded that elemental iodine hydroalcoholic solution (iodine tincture) is effective for first aid use on minor wounds as a skin antiseptic, skin wound protectant, and skin wound cleanser, although questions remained regarding the minimally effective dose and the effect of organic load and pH. In addition, the agency was concerned about the irritating properties of iodine and delay in wound healing and therefore classified iodine tincture in Category III (43 FR 1210 at 1234).

The agency has reviewed the data and information submitted by the comments (Refs. 1 and 2), which described reports from studies on the properties of elemental iodine, iodine tincture U.S.P., and iodine solution U.S.P. The studies, not previously reviewed in either the Panel report or in the tentative final monograph, provided data primarily pertaining to effectiveness.

The agency has also considered additional studies in test wounds of laboratory animals. Branemark et al. (Ref. 3) inflicted minute test wounds and control wounds in the skin of mice, hamsters, and rabbits. The test wounds were treated with iodine solutions, and the structure of the skin was observed microscopically for healing. Various antiseptic ingredients, including iodine in saline solution, were tested on minute cutaneous wounds. Microscopic analysis showed very slight tissue injury from the antiseptic.

Edlich et al. (Ref. 4) inflicted deep wounds in the skin of guinea pigs, contaminated the wounds with *S. aureus*, waited 5 minutes, cleansed the wounds with 100 milliliters (mL) of various antiseptic solutions, including 70 percent alcohol, iodine aqueous solution or iodine tincture, and saline control solutions. The wounds were closed with tape, observed, and measured for inflammatory responses (i.e., induration and pus). Subcultures were made for viable bacteria. Edlich et al. reported that 70 percent alcohol, iodine aqueous solution, and iodine tincture helped to reduce the rate of infection without causing significant inflammatory responses in the wounds. Specifically, the authors stated that "The gross infection score, the indurated wound margin, and the percentage of positive cultures in the contaminated wound receiving a single irrigation with tincture of iodine were significantly less than the corresponding inflammatory responses in the control wounds."

Based on the available data, the agency concludes that 2 percent aqueous or alcoholic solutions of elemental iodine (i.e., iodine tincture, U.S.P. or iodine topical solution, U.S.P.) are safe and effective for first aid use to decrease the number of bacteria in minor cuts and scrapes. Therefore, the agency is proposing that these iodine solutions be Category I for use as a first aid antiseptic.

References

(1) Salle, A. J., and B. W. Catlin, "Profile Evaluations of Germicides," *Journal of the American Pharmaceutical Association*, (Scientific Edition), 36:129–133, 1947.

(2) Gershenfeld, L., and B. Witlin, "Iodine as an Antiseptic," Annals of the New York Academy of Sciences, 53:172–182, 1950.

(3) Branemark, P. J., et al. "Tissue Injury Caused by Wound Disinfectants," Journal of Bone and Joint Surgery, 49:48–62, 1967.

(4) Edlich, R. F., et al., "Studies in Management of the Contaminated Wound, III. Assessment of the Effectiveness of Irrigation with Antiseptic Agents," The American Journal of Surgery, 118:21–30, 1969.

38. A number of comments submitted new data (Ref. 1) to establish that povidone-iodine is safe and effective as a topical antimicrobial drug. The comments requested that povidone-iodine be reclassified from Category III to Category I as a topical antimicrobial ingredient for use as an antimicrobial soap, health-care personnel handwash, surgical hand scrub, patient preoperative skin preparation, skin antiseptic, skin wound cleanser, and skin wound protectant.

The agency has considered the new povidone-iodine data submitted in support of the request to reclassify povidone-iodine from Category III to Category I as well as the reports of other advisory panels. On the basis of this information FDA has tentatively concluded that povidone-iodine should be classified in Category I for use as a first aid antiseptic.

The Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products, in its report published October 13, 1983, stated that "microbiocidal effectiveness of povidone-iodine has been clearly demonstrated by in vitro studies against a variety of pathologic bacteria, fungi, and protozoan organisms" and "in clinical studies, povidone-iodine has been shown to disinfect skin and mucous membrane" (48 FR 46694 at 46705). That Panel classified povidone-iodine diluted to 0.15 to 0.30 percent for use as a douche as Category I for the "relief of minor irritation of the vagina" but reserved directions for use of full-strength solution for professional uses.

The Antimicrobial II Panel reviewed povidone-iodine as a topical antifungal ingredient. In its evaluation, the Panel relied on new safety data as well as the recommendations of the Antimicrobial I Panel in the **Federal Register** published September 13, 1974 (39 FR 33103 at 33129). The Antimicrobial II Panel's recommendations on antifungal use of povidone-iodine were published in the March 23, 1982 **Federal Register** (47 FR 12480 at 12545) as an advance notice of proposed rulemaking. That Panel concluded that 10 percent povidone-iodine was safe for OTC topical antifungal use in the treatment of athlete's foot, jock itch, and ringworm.

The safety aspects of povidone-iodine as a topical first aid antiseptic for consumer use in the home environment (short-term use over limited areas of the skin) are essentially the same as those described by the Antimicrobial II Panel for topical antifungal ingredients. The agency concurs with and adopts the Antimicrobial II Panel's safety evaluation of povidone-iodine. Povidone-iodine is being proposed as generally recognized as safe as an OTC topical first aid antiseptic ingredient in this amended tentative final monograph. (See comments 41 and 42 for additional safety discussions. See comment 39 for effectiveness discussion.)

Reference

(1) Comments No. C00104, C00108, C00111, C00112, C00113, C00128, C00132, and C00133, Docket No. 75N–0183, Dockets Management Branch.

39. Several comments requested that the tentative final monograph specify the lowest potency concentration of available iodine that marketed preparations be allowed to reach before

being considered ineffective and, thus, adulterated or misbranded (Refs. 1 to 4). One comment (Ref. 2) asserted that "many noncompendial povidone-iodine preparations do not specify the labeled amount of iodine, and there is wide variation in their potency. This has created confusion in the market and may put consumers at risk." The comment requested "that those preparations which are placed in Category I contain in the respective use monograph a lower potency limit, irrespective of the original concentration, since this lower limit would still be effective." Another comment (Ref. 3) suggested that the monograph be revised to include povidone-iodine as an antimicrobial bar soap containing not less than 5 percent nor more than 10 percent povidone-iodine U.S.P., equivalent to 0.5 percent and 1.0 percent available iodine. Topical dosage for use as a solution containing not less than 7.5 percent nor more than 10 percent povidone-iodine U.S.P., equivalent to 0.75 percent and 1.0 percent available iodine, was proposed for a health-care personnel hand wash, surgical hand scrub, skin antiseptic, skin wound cleanser, skin wound protectant, or a patient preoperative skin preparation.

One comment (Ref. 4) included data on the rate of release of iodine from povidone-iodine to support effectiveness.

In the previous tentative final monograph, the agency did not discuss or recommend specific concentrations of povidone-iodine for the proposed seven classes of preparations (i.e., antimicrobial soap, health-care personnel handwash, surgical hand scrub, skin antiseptic, skin wound cleanser, skin wound protectant, and patient preoperative skin preparation) (43 FR 1210 at 1235). However, the agency stated that "the question of iodine release from the complexed molecule, including rate of release and binding to other materials, as well as the influence of the release rate on effectiveness, must be resolved" (43 FR 1236).

Subsequently, the agency has reviewed chemical data and in vivo and in vitro biological data that support the effectiveness of povidone-iodine (Refs. 1 through 4). The biological data show that dilutions from marketed 5 percent povidone-iodine and marketed 7.5 to 10 percent povidone-iodine significantly reduced the number of test bacteria within 1 minute (Refs. 1 and 2). According to references that were submitted in connection with another rulemaking, povidone-iodine solution at concentrations of 1 to 10 percent contains over 99 percent complexed iodine (Ref. 5). Based on an iodine-starch reaction as a biological model, it has been shown that any iodine that is removed from the complex would be replaced within less than 25 milliseconds (Ref. 6). The agency's detailed evaluation is on display in the Dockets Management Branch (Ref. 7).

The data show that as the already released iodine interacts chemically with the microbes, more iodine is rapidly released from the povidone-iodine. Consequently, the availability of the iodine is not a problem. Furthermore, povidone-iodine manufactured in accordance with current good manufacturing practices (21 CFR Part 211) should not present problems. Based on the available data, povidone-iodine at 5 to 10 percent concentrations is being classified as Category I for first aid antiseptic use.

Other uses for povidone-iodine will be addressed separately in the segment of this rulemaking dealing with uses other than first aid in a future issue of the **Federal Register.**

References

(1) Comment No. C00104, Docket No. 75N–0183, Dockets Management Branch.

(2) Comment No. C00128, Docket No. 75N–0183, Dockets Management Branch.

(3) Comment No. C00103, Docket No. 75N–0183, Dockets Management Branch.

(4) Comment No. C00111, Docket No. 75N–0183, Dockets Management Branch.

(5) Schenck, H.U., et al., "Structure of Povidone-Iodine," *in* "Current Chemotherapy and Infectious Disease," Volume I, American Society for Microbiology, Washington, pp. 477–478, 1980.

(6) Ditter, W., D. Horn, and E. Luedekke, "Thermodynamic and Kinetic Examinations Concerning the Complex Binding State and the Rate of Liberation of Iodine from Aqueous Iodine-PVP-Solutions," included in Comment No. C00012, Docket No. 81N–0014, Dockets Management Branch.

(7) Letter from W. E. Gilbertson, FDA, to L. Blecher, GAF Corp., October 5, 1983, Coded LET004, Docket No. 81N–0114, Dockets Management Branch.

40. Several comments objected to FDA's requiring expiration dates (not to exceed 2 years after manufacture) for all products containing an iodophor active ingredient (43 FR 1210 at 1235). The comments stated that stability varies among different iodophor products, with some products falling short of, and others far exceeding, this time period. The comments argued that data derived from a particular formulation are not applicable to other iodophor categories or even to formulations containing a common active ingredient because of the nature of the particular formulation, the purity of the active ingredient, other substances used, and the level of manufacturing expertise available.

The comments also pointed out that the fixed 2-year time period is contrary to FDA's policy under the good manufacturing practice regulations, which require that the stability profile of each individual product in its own container-closure system under varying environmental conditions be known and controlled. The comments argued that it is important that expiration dating for iodophor products be supported by each manufacturer, with well-defined test data, for the stability term that is proposed for a particular formulation and that such support data should include studies conducted under conditions of actual use demonstrating that the formulation is stable for the period claimed.

The agency agrees with the comments. At the time the agency proposed expiration dates, the agency was concerned with the lack of stability data submitted for the several iodophor preparations. However, current good manufacturing practice regulations (21 CFR parts 210 and 211) require a testing program to assess the stability of finished products and to determine appropriate storage conditions and an expiration date. Under § 211.137, drug products must bear an expiration date supported by reliable stability data. The agency has proposed an exemption from this requirement for human OTC products that do not bear dosage limitations if appropriate data show that the products are stable for at least 3 years. (See § 211.137(g).) Because of these current good manufacturing practice regulations, the agency concludes it is not necessary to include specific expiration dating periods for dosage forms of povidone-iodine or other iodophors in the amended tentative final monograph. Therefore, the previously proposed 2-year expiration date for iodophors has been eliminated.

41. Several comments submitted data from published and unpublished studies to show that povidone-iodine does not alter thyroid function (Refs. 1 through 12). These data were submitted in response to FDA's request for controlled research to show the conditions of use under which thyroid function would, or would not, be altered (43 FR 1210 at 1235). The comments stated that although the data show that the amount of total serum iodine, or iodide, is increased after povidone-iodine is used topically, there is no significant alteration of the level of thyroid hormone measured by RT_3U, T_3, and T_4 radioimmunoassays.

One comment pointed out that, as part of the ongoing review of food additives, FDA issued a final order on March 31, 1978 (43 FR 11699) (21 CFR 184.1634) confirming that potassium iodide, a salt of iodine, is generally recognized as safe. The comment also pointed out that, in a separate rulemaking procedure for OTC vitamin and mineral drug products (44 FR 16126 at 16181), the Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic Drug Products discussed the safety of iodine and advised that the thyroid can safely absorb up to 2 milligrams of iodine without metabolizing it. This absorption prevents the accumulation of iodine that would inhibit thyroid hormone synthesis. The comment added that the administrative record for the antimicrobial monograph contains adequate data to show that topically applied iodine is virtually not absorbed.

The agency has reviewed the data submitted (Refs. 1 through 12) and agrees with the comments that thyroid dysfunction does not occur from the topical use of povidone-iodine. Plasma iodine levels may be elevated following the topical use of povidone-iodine; however, the thyroid adapts to the iodine elevation, and the iodine is readily excreted by the kidney without evidence of thyroid dysfunction. During a study of the effects of surgical scrubbing with povidone-iodine for 2 weeks, it was concluded that some absorption of iodine did occur when povidone-iodine was used topically (Ref. 12). The serum iodine concentration was elevated, but not protein-bound iodine, T_4, T_3, or TSH. However, the level of serum iodine returned to normal when povidone-iodine use was discontinued. In addition, studies following the application of povidone-iodine to the mucous membranes (vagina) and intact and damaged skin in humans and animals reported protein-bound iodine elevations, but no alterations in thyroid function (Refs. 4, 7, 9, and 10). Therefore, the agency believes that topically applied povidone-iodine does not cause thyroid dysfunction and is safe for OTC use.

References

(1) Alden, E.R., et al., "Effect of Prenatal Povidone-Iodine Perineal Antisepsis on Serum Protein-Bound Iodine," Obstetrics and Gynecology, 35:253–254, 1970.

(2) Garnes, A.L., et al., "Clinical Evaluation of Povidone-Iodine Aerosol Spray in Surgical Practice," American Journal of Surgery, 97:49–53, 1959.

(3) Goldman, M., and D. Landry, "The Effect of Povidone-Iodine on Thyroid Function in Rats," Toxicology and Applied Pharmacology, 35:341–346, 1976.

(4) Gortz, G., "Povidone-Iodine (Mundidone)—Alternative to Topical Antibiotics: Effects and Side Effects in Wound Treatment," 10th International Congress of Chemotherapy, Zurich, 1977.

(5) Higgins, H.P., et al., "The Effect of Povidone-Iodine (Betadine) on Serum Protein-Bound Iodine, When Used as a Surgical Preparation on Intact Skin," The Canadian Medical Association Journal, 90:1298–1300, 1964.

(6) Kearns, J.E., "The Effect of New Iodophors on Protein-Bound Iodine and Butinol Extractable Iodine in Humans," American Journal of Surgery, 109:457–459, 1965.

(7) King, I.R., and A.W. Diddle, "Protein-Bound Iodine and T_4 Tests After Vaginal Application of Povidone-Iodine," American Journal of Obstetrics and Gynecology, 108:1175–1177, 1970.

(8) Lavelle, K.J., et al., "Iodine Absorption in Burn Patients Treated Topically with Povidone-Iodine," Clinical Pharmacology and Therapeutics, 17:355–362, 1975.

(9) Meissner, K., et al., "Povidone-Iodine Versus Antibiotic Application in Prophylaxis and Treatment of Peritonitis: Effects on Thyroid Function," 10th International Congress of Chemotherapy, Zurich, 1977.

(10) Quagliana, J.M., "Effect of Topical Povidone-Iodine (Betadine) on Serum Protein-Bound Iodine," Journal of Clinical Endocrinology and Metabolism. 23:395–397, 1963.

(11) Renk, E., et al., "The Influence of Povidone-Iodine (Mundidone) on the PBI and BEI Serum Levels in Burn and Peritonitis Therapy," 10th International Congress of Chemotherapy, Zurich, 1977.

(12) Ingbar, S.H., "Studies of the Effects of Surgical Scrubbing with PVP–I," unpublished study included in Comment No. C0032, Docket No. 75N–0183, Dockets Management Branch.

42. Several comments objected to the Commissioner's statement in the antimicrobial tentative final monograph that data presented to the Panel suggested that nonsurfactant iodophor products (povidone-iodine) delay the rate of wound healing (43 FR 1210 at 1235). One comment submitted new data to show that povidoneiodine has no adverse effect on wound healing in animals or humans (Refs. 1 through 13). Another comment stated that povidoneiodine may, in fact, aid wound healing.

The agency has reviewed the new data submitted by the comments and agrees that povidone-iodine does not delay wound healing. Controlled studies on wound healing were conducted in animals and humans and involved various types of dermal wounds and several antiseptics, including povidone-iodine. Both superficial and deeper wounds were studied with a contralateral control, and clinical evaluation was also done on patients receiving split-skin grafts. Results showed that there were no statistically significant differences in mean healing times between any of the treatment groups and their saline controls. In addition, microscopic analysis showed no differences in wound healing in the groups studied. These pathological and histological studies did not indicate any deleterious effect of povidone-iodine on wound healing. However, there was also no evidence demonstrating that povidone-iodine might aid wound healing.

References

(1) Paster, Z., "A Study of the Effect of Polydine on Wound Healing," Israel Institute for Biological Research, 1977, unpublished study, EXT012, Docket No. 75N–0183, Dockets Management Branch.

(2) Gruber, R.P., L. Vistnes, and R. Pardoe, "The Effect of Commonly Used Antiseptics on Wound Healing," Plastic and Reconstructive Surgery, 55:472–478, 1975.

(3) Gilmore, O.J.A., "A Reappraisal of the Use of Antiseptics in Surgical Practice," Annals of the Royal College of Surgeons of England, 59:93–103, 1977.

(4) Gilmore, O.J.A., C. Reid, and A. Strokon, "A Study of the Effect of Povidone-Iodine on Wound Healing," Postgraduate Medical Journal, 53:122–125, 1977.

(5) Sindelar, W.F., and G.R. Mason, "Irrigation of Subcutaneous Tissue with Povidone-Iodine Solution for Prevention of Surgical Wound Infections," Surgery Gynecology and Obstetrics, 148:227–231, 1979.

(6) Gilmore, O.J.A., "Prevention of Wound Infection," Lancet, 1:1134, 1973.

(7) Gilmore, O.J.A., and T.D.M. Martin, "Aetiology and Prevention of Wound Infection in Appendectomy," British Journal of Surgery, 61:281–287, 1974.

(8) Gilmore, O.J.A., et al., "Colonic Anastomosis Healing: The Effect of Topical Povidone-Iodine," European Surgical Research, 10:94–104, 1978.

(9) Gilmore, O.J.A., and P.J. Sanderson, "Prophylactic Interparietal Povidone-Iodine in Abdominal Surgery," British Journal of Surgery, 62:792–799, 1975.

(10) Gilmore, O.J.A., "Intraperitoneal Povidone-Iodine," Lancet, 2:37–38, 1977.

(11) Morgan, W.J., "Povidone-Iodine Spray for Wounds Sutured in the Accident Department," Lancet, 1:769, 1978.

(12) Gilmore, O. J. A., et al., "Prophylactic Intraperitoneal Povidone-Iodine in Alimentary Tract Surgery," American Journal of Surgery, 35:156–159, 1978.

(13) Gilmore, O. J. A., "Experimental Treatment of Peritonitis and Peritoneal Adhesions with Antiseptics," in "Proceedings of the World Congress on Antiseptics," Limburg/Lahm, Germany, pp. 117–119, 1976.

43. Several comments requested clarification of contradictory statements concerning the compatibility of iodophors in antimicrobial soaps. The agency agreed to delete the statement of incompatibility of povidone-iodine in soap formulation (43 FR 1210 at 1221; comment 70), but then at 43 FR 1236 the agency stated that it was unaware of any data to show that iodophors can be

formulated into antimicrobial soaps. Another comment pointed out that the agency's conclusion at 43 FR 1236 was inconsistent with the list of Category III active ingredients at 43 FR 1229. One comment also requested that poloxamer-iodine complex be deleted from the Category II list for antimicrobial soaps at 43 FR 1227 because there are no stability differences between povidone-iodine and poloxamer-iodine complexes. The comment pointed out that both complexes are currently being marketed as stable products in synthetic soap formulations and argued, therefore, that poloxamer-iodine complex should be made Category III, as was povidone-iodine complex.

The statement regarding incompatibility of iodophors, such as povidone-iodine, that appeared at 43 FR 1236 was in error. The response to comment 70 (43 FR 1221) was correct in stating that povidone-iodine can be formulated in soaps without incompatibility problems. In addition, the list of Category III active ingredients at 43 FR 1229 correctly listed povidone-iodine as a Category III antimicrobial soap. The agency recognizes that both povidone-iodine and poloxamer-iodine complexes can be formulated in soaps without encountering stability problems and will address soap formulations of both complexes in a future issue of the Federal Register. (See comment 19.)

J. Comments on Quaternary Ammonium Compounds (quats)

44. One comment requested that benzalkonium chloride be placed in Category I as a skin antiseptic, a patient preoperative skin preparation, and a skin wound protectant, in addition to its present Category I classification as a skin wound cleanser. In support of its request, the comment cited several surgery textbooks and other references that recommend use of benzalkonium chloride at concentrations ranging from 1:750 to 1:5,000 as a preoperative skin preparation, surgical scrub, skin antiseptic for venipuncture, and in urinary tract procedures, especially in catheterized patients (Ref. 1). The comment also submitted 2 studies on a product containing benzalkonium chloride at a concentration of 1:1,000: (1) an in vitro study to demonstrate that this product formulation acts as a physical chemical barrier against contamination by microorganisms, and (2) a study on induced wounds on the arms of 10 healthy subjects to present evidence that this product is nonirritating and neither delays healing nor favors the growth of microorganisms (Ref. 2).

In the previous tentative final monograph, a 1:750 (0.13 percent) use concentration of benzalkonium chloride was proposed as a Category I "skin wound cleanser" (43 FR 1220 at 1236 to 1237). However, this concentration of benzalkonium chloride was categorized as Category III for other uses requested by the comment, i.e., "skin antiseptic," "skin wound protectant," and "patient preoperative skin preparation." The agency stated that it was "not seriously concerned with the safety of 'quats' for 'first-aid' uses, i.e., in skin wound cleansers, skin wound protectants, and skin antiseptics" (43 FR 1236). The agency also stated that "before 'quats' in general can be finally classified for such uses, the following minor issues must be resolved: delay of skin wound repair, contact dermatitis, and sensitivity to 'quats' " (43 FR 1236). The agency limited the use concentration to not greater than 1:750 and advised that data are needed to establish the minimum and maximum concentrations to be included in the monograph. (See comment 53, 43 FR 1219, and 43 FR 1236 to 1237.)

In this amended tentative final monograph for first aid antiseptic drug products, the agency is combining the former categories "skin wound cleaner," "skin wound protectant," and "skin antiseptic" into a new category "first aid antiseptic." (See comment 13.) The other uses for benzalkonium chloride requested by the comment, e.g., "patient preoperative skin preparation" will be addressed in the segment of this rulemaking dealing with uses other than first aid in a future issue of the Federal Register.

The agency has evaluated the scientific review of published articles (Ref. 1), as well as data from safety and effectiveness studies on a product containing benzalkonium chloride (Ref. 2). In the studies of the benzalkonium chloride product (1:1000 (0.10 percent)), uniform superficial wounds were made by the ammonium hydroxide blister method on the forearms of each of 10 human test subjects. Tests wounds were treated three times daily for 3 days with benzalkonium chloride and occluded. The control site was untreated and occluded. Quantitative evaluations of resident skin bacteria recovered from test wound and control wound sites demonstrated that benzalkonium chloride significantly reduced the resident bacteria (i.e., 1 $\log_{10}$). In addition, the study showed that although the treated wounds showed a greater degree of erythema than the untreated wounds on observation days 3 and 5, no other significant differences were observed for crust/scab formation, erythema, or epithelization. The agency believes that these data show that benzalkonium chloride is nonirritating and does not interfere with healing of minor wounds.

Based on the new data, the agency concludes that the safe and effective range for benzalkonium chloride has been established between 0.1 percent to 0.13 percent. Because the concerns that the agency raised in the previous tentative final monograph have now been satisfactorily resolved, the agency is including benzalkonium chloride (1:1000, 0.1 percent to 1:750, 0.13 percent) in this tentative final monograph for first aid antiseptic drug products.

References

(1) "Benzalkonium chloride (Zephiran)," unpublished report submitted by Sterling Drug, Inc., Comment No. C00116, Docket No. 75N-0183, Dockets Management Branch.

(2) Unpublished Clinical Wound Healing Studies on Medi-Quik® submitted by Sterling Drug, Inc., Comment No. SUP013, Docket No. 75N-0183, Dockets Management Branch.

45. One comment objected to the 1:750 use concentration limit established for quaternary ammonium compounds in proposed § 333.40(a). The comment submitted safety and efficacy data for a product with a 1:200 concentration of methylbenzethonium chloride, a quaternary ammonium compound. The comment stated that these studies, as well as previously submitted data and a long history of marketing use for this product, demonstrate that this ingredient is safe for consumer use at this concentration. The comment contended that the 1:750 use concentration limit selected by FDA is completely arbitrary and requested that a Category I skin wound cleanser classification be given to this 1:200 concentration of methylbenzethonium chloride.

As discussed in comment 13, skin wound cleansers have been incorporated into a broader group of antimicrobial containing drug products that are designated as first aid antiseptics in this tentative final monograph. The agency has reviewed several reports previously reviewed by the Panel and new material submitted since the Panel report was published, including the data submitted with this comment in the context of this new category. Based on a review of these data, the agency concludes that the 1:200 (0.5 percent) concentration of methylbenzethonium chloride is safe and effective for first aid use on minor cuts, scrapes, and burns.

Apparently, in its original evaluation of these data on methylbenzethonium chloride, the Panel overlooked the 1:200 concentration and referred only to the usual marketed 1:750 concentration of benzalkonium chloride (0.13 percent) as the standard for all quaternary ammonium compounds. The data show that a 0.5-percent concentration of methylbenzethonium chloride is safe and nonirritating. Human studies by Killian (Ref. 1) and by Withers and Hale (Ref. 2) utilizing 0.5 percent methylbenzethonium chloride indicated that the product did not show any significant primary skin irritation, skin fatigue, or sensitization. A study by Vignec (Ref. 3) provided further support that the drug is safe and nonirritating. Vignec used 0.5 percent methylbenzethonium chloride solution full strength on 138 infants suffering from diaper irritation, minor skin conditions, and excoriation and concluded that the drug was safe and nonirritating. The fact that the solution of methylbenzethonium chloride was used under the occlusion of a diaper without evidence of irritation strongly suggests the safety of this concentration.

Maibach (Ref. 4) reported that, even after a 21-day application of 0.5 percent methylbenzethonium chloride under occlusion, minimal irritation was observed. In this study, a 2- by 2-centimeter patch of nonwoven fabric impregnated with 0.2 mL of methylbenzethonium chloride solution was applied to each subject's back and occluded with tape. The patch was removed every 24 hours. After the test site was read, a freshly medicated patch was applied to the same area. The cumulative irritation index score for the 0.5 percent methylbenzethonium chloride preparation was 8.19 and 5.50 out of a possible score of 84. A second study by Maibach (Ref. 5) on 200 subjects used the standard Draize human sensitization test. The investigator concluded that there was no evidence of contact sensitization to the product. Therefore, the agency concludes that a concentration range of 1:750 (0.13 percent) to 1:200 (0.5 percent) of methylbenzethonium chloride is safe and nonirritating as a first aid antiseptic.

The agency's detailed comments and evaluation of the data and the references are on file in the Dockets Management Branch (Ref. 6).

References

(1) Killian, J. A., "Summary of Local Irritation Actions on Skin and of Sensitizing Properties of Bactine," Section II–A, unpublished report to Miles Laboratories, Inc., 1949, OTC Vol. 020088.

(2) Withers, O. R., and R. Hale, "Skin Tests to Bactine on Hypersensitive Patients," unpublished report to Miles Laboratories, Inc., 1951, OTC Vol. 020088.

(3) Vignec, A. J., "Treatment of Diaper Rash," unpublished report to Miles Laboratories, Inc., 1952, OTC Vol. 020088.

(4) Maibach, H. I., "21-Day Cumulative Irritancy Assay," unpublished report, Miles Medical Department Study No. 2213, 1977, Exhibit 6 of SUP014, Docket No. 75N–0183, Dockets Management Branch.

(5) Maibach, H. I., "Modified Draize Human Sensitization—200 Subjects," unpublished report, Miles Medical Department Study No. 2226, 1978, Exhibit 8 of SUP014, Docket No. 75N–0183, Dockets Management Branch.

(6) Letter from W. E. Gilbertson, FDA, to E. B. Peel, Miles Laboratories, Inc., coded LET 038, Docket No. 75N–0183, Dockets Management Branch.

K. Comment on Tribromsalan

46. One comment stated that tribromsalan in its commercially pure form is not a photosensitizer and submitted an unpublished study to support its contention (Ref. 1). In the study the test agent was applied to 25 subjects for 24 hours, followed by exposure to three Minimal Erythema Doses of solar-simulated radiation twice weekly for 3 weeks. The subjects were challenged 10 to 14 days after the last exposure, and the reactions were evaluated 48 and 72 hours later. The study results demonstrated that pure tribromsalan did not cause photocontact allergy, whereas tribromsalan containing 45 percent dibromsalan did. The investigators speculated that the photosensitizing potential attributed to tribromsalan is caused by the presence of dibrominated contaminants.

In addition, the comment included a statement from an expert who had testified before the Panel. This expert had maintained that photosensitization attributable to tribromsalan had not occurred recently and that any earlier cases attributed to tribromsalan were probably due to cross-reactions in patients sensitized to ingredients such as dibromsalan, bithionol, and tetrachlorosalicylanilide or, less likely, hexachlorophene or dichlorophen. The comment requested that tribromsalan be removed from Category II status.

In the **Federal Register** of October 30, 1975 (40 FR 50527), FDA issued a final regulation (21 CFR 310.503) declaring any drug product containing certain halogenated salicylanilides (including tribromsalan) to be a new drug, stating that these ingredients are not generally recognized as safe and effective for use as active or inactive ingredients in any drug product. The study submitted with the comment does not contain sufficient new information to allow the agency to consider tribromsalan generally recognized as safe and effective for OTC drug use. The submitted study, which has since been published (Ref. 2), showed that 2 of the 25 subjects became photosensitized with the sample of tribromsalan containing 45 percent dibromsalan, whereas no subjects had a reaction to the more purified sample of tribromsalan. One of the two subjects who was photosensitized to the tribromsalan that contained dibromsalan developed cross-reactions to the purer sample of tribromsalan. Five subjects who were sensitized by tetrachlorosalicylanilide also showed cross-reactivity to the purer sample of tribromsalan.

When the regulation was published in 1975, the agency recognized that manufacturing limitations for tribromsalan used in earlier formulations resulted in contamination with higher concentrations of more potent photosensitizing chemical impurities, such as dibromsalan and metabromsalan. The agency also noted that the level of impurities was reduced with improved manufacturing techniques and that tribromsalan sensitization was declining, but had not disappeared. In addition to the problem of photosensitization, the agency was concerned about the lack of toxicological data adequate to establish a safe level for use. Another concern was the adverse benefit-to-risk ratio. (See 40 FR 50527 at 50528 and 50530.) In the absence of adequate data to answer these concerns, the provisions of the regulation in § 310.506 for tribromsalan remain in effect. A new drug application containing appropriate toxicological and manufacturing controls information may be submitted to obtain marketing approval for any product containing tribromsalan.

References

(1) Kaidbey, K. H., and Kligman, A. M., "The Photomaximization Test for Identifying Photoallergic Contact Sensitizers," unpublished study, Comment No. C00095, Docket No. 75N–0183, Dockets Management Branch.

(2) Kaidbey, K. H., and Kligman, A. M., "The Photomaximization Test for Identifying Photoallergic Contact Sensitizers," Contact Dermatitis, 6:161–169, 1980.

L. Comments on Triclocarban

47. Several comments requested Category I status for triclocarban as an active ingredient in antimicrobial soaps and presented new safety data. These data included information to elucidate the metabolic pathways and the pharmacokinetics of triclocarban, short-term toxicity data in animals to determine the target organ for toxicity

and the effect and no-effect levels of use (Ref. 1), long-term toxicity data in animals (Ref. 2), and metabolism data in neonate monkeys (Ref. 3). The comments argued that the data confirmed historical experience showing that triclocarban can be safely used in soaps by infants and adults.

The agency has evaluated data and information submitted by the comments and advised a manufacturer that the study entitled "Twenty-Four Month Dietary Toxicity/Carcinogenicity Study of TCC in Rats" (Ref. 2) served to resolve the agency's safety concern regarding blood levels, target organ toxicity, and no effect levels (43 FR 1210 at 1233) and that triclocarban can be recognized as safe for OTC daily topical use in a concentration of 1.5 percent (Ref. 4). However, as stated in comments 10 and 26, antimicrobial soaps making only cosmetic claims are no longer being considered in this rulemaking.

In the previous tentative final monograph, triclocarban (1.5 percent) was categorized in Category III as a skin wound cleanser, and in Category II as a skin antiseptic and skin wound protectant. However, as discussed in comment 13, the agency is no longer using the product category designations of skin antiseptics, skin wound protectants, and skin wound cleansers. Instead, those product categories have been combined into a first aid antiseptic category. The agency has reassessed data that were discussed in the Panel's report (Refs. 1 and 3, 39 FR 33103 at 33125) in light of the first aid antiseptic category, and is proposing a Category III classification for effectiveness for triclocarban (1.5 percent) not in soap forms for use as a first aid antiseptic.

References

(1) Comments No. SUP018, C00099, C00115, and CP0002, Docket No. 75N–0183, Dockets Management Branch.

(2) Comments No. SUP041 and CP0004, Docket No. 75N–0183, Dockets Management Branch.

(3) Comments No. MM0005 and LET047, Docket No. 75N–0183, Dockets Management Branch.

(4) Letter from W. E. Gilbertson, FDA, to G. Roush, Jr., Monsanto Co., coded LET032, Docket No. 75N–0183, Dockets Management Branch.

M. Comments on Triclosan

48. A number of comments submitted data and information from microbiological, mutagenicity, metabolism, cross-sensitization, photosensitization, and drug experience studies on triclosan (Ref. 1). The comments stated that the data and information show that triclosan (up to 1.0 percent) is safe and effective and that triclosan should be placed in Category I for use in the categories that were defined in the previous tentative final monograph, i.e., skin antiseptic, skin wound cleanser, skin wound protectant, antimicrobial soap, health-care personnel handwash, patient preoperative skin preparation, and surgical hand scrub. In addition, one comment submitted information on triclosan (0.1 percent) for the treatment of diaper rash and on triclosan (0.1 percent) combined with benzocaine for the treatment of sunburn (Ref. 2).

One comment from the manufacturer of triclosan objected to the agency's expressed concern, as stated in the tentative final monograph (43 FR 1210 at 1231 and 1233), that there is proliferation of products containing triclosan marketed to the American consumer (Ref. 3). Arguing that the agency's concerns were without factual basis, the comment submitted sales data, held confidential under 21 CFR 10.20(j)(2)(i)(*d*), showing that overall sales of triclosan in the United States have in fact decreased from 1973 to 1977 and that sales for use in bar soaps and deodorants have also declined from 1973 to 1977. The comment pointed out that it has exclusive United States patent rights for triclosan and that no license has been, or will be, granted under these patents. The comment added that to the best of its knowledge triclosan is not used in infant clothing, a use mentioned in the tentative final monograph (43 FR 1231). The comment stated that if triclosan is placed in Cateqory I for use in antimicrobial soaps, it would limit sales of triclosan to OTC use in antimicrobial and deodorant soaps, underarm deodorants, and registered Environmental Protection Agency (EPA) pesticide products. In the future, sales might be extended to include approved new drug applications. The comment also pointed out that the statement at 43 FR 1233 about the EPA's Office of Special Pesticide Review preparing a report on the proliferation of triclosan-containing products is in error, and that the erroneous statement apparently resulted from a miscommunication between FDA and EPA staff. The comment concluded that the concerns about proliferation raised by the agency in the tentative final monograph should not prevent triclosan from being placed in Category I.

Another comment from the manufacturer of triclosan submitted validation reports and raw data from a 2-year chronic oral toxicity study in rats, and carcinogenicity and reproduction studies conducted in mice, rats, rabbits, and monkeys by Industrial Bio-Test Laboratories (IBT) (Refs. 4, 5, and 6) and asserted that its validation of the studies shows that triclosan is safe.

Several comments objected to the agency's restriction that antimicrobial soaps containing triclosan can only be formulated in a bar soap to be used with water (43 FR 1210 at 1229) (Ref. 1). The comments argued that such a restriction was not applied to the other Category III uses of triclosan, i.e., skin antiseptic, skin wound cleanser, and skin wound protectant, and that such a restriction was not recommended by the Panel in the advance notice of proposed rulemaking. The comments suggested that the footnote under "antimicrobial soaps" limiting triclosan to bar soap was probably intended to apply to cloflucarban, which, like triclocarban, is known for its "physical and/or chemical incompatibility."

With regard to safety, the agency evaluated the validation reports to support long-term use of the ingredient (Refs. 4, 5, and 6) and advised the manufacturer of triclosan that the IBT studies were invalid because of numerous problems. The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 7).

The manufacturer subsequently stated its intent to no longer rely on the 2-year chronic oral toxicity IBT study (Ref. 8), and submitted a final report from a new 2-year chronic oral toxicity study in rats (Ref. 9). Pending completion of the agency's evaluation of this new 2-year study, triclosan remains classified in Category III for safety for long-term use.

The agency has evaluated other data and information (Ref. 1) and advised the same manufacturer that these studies resolved the agency's safety concerns for short-term use of triclosan when used in concentrations up to 1.0 percent, but that additional effectiveness data were needed before the ingredient could be placed in Category I. The agency's detailed comments are on file in the Dockets Management Branch (Ref. 10). In a response to the agency, the manufacturer of triclosan requested further guidance, included effectiveness data from in vivo studies for chronic uses (i.e., antimicrobial soap, health care personnel handwash, and surgical hand scrub), and requested that in future rulemaking proceedings, triclosan (being bacteriostatic and not bacteriocidal) either be excluded from categorization or designated "not applicable" for short-term uses as a patient preoperative skin preparation, skin antiseptic, skin wound cleanser, and skin wound protectant (Ref. 11).

In view of the new category "first aid antiseptic" and the effectiveness criteria in proposed § 333.10 (see comment 57), the agency is tentatively classifying triclosan as Category III for effectiveness as a first aid antiseptic. The use of triclosan as a health care personnel handwash, patient preoperative skin preparation, and surgical hand scrub and safety for chronic use will be addressed in the non-first aid segment of this rulemaking dealing with uses other than first aid in a future issue of the **Federal Register**. The use of triclosan for the treatment of diaper rash was addressed in the **Federal Register** of June 20, 1990 (55 FR 25246 at 25277). The use of triclosan for the treatment of sunburn will be addressed in another OTC drug rulemaking covering drug products for this use.

The agency has communicated further with EPA and has ascertained that there is no specific report on the proliferation of triclosan (Ref. 12). Regarding exclusive patent rights, the agency advises that these are not among the determining criteria to establish general recognition of safety and effectiveness, and therefore cannot be used in the evaluation. However, having reviewed the new data along with the previously submitted data, the agency concludes that there is no proliferation problem with triclosan.

Finally, the agency did not intend to restrict formulations of triclosan to bar soap. The agency has reviewed the Panel's recommendations and the footnotes in the previous tentative final monograph (43 FR 1210 at 1229) and finds that triclosan under "antimicrobial soaps" was erroneously marked with the reference to the footnote "Category III only when formulated in a bar soap to be used with water."

References

(1) Comments No. CP0001, SUP019, SUP023, C00103, C00109, SUP031, SUP039, and C00134, Docket No. 75N–0183, Dockets Management Branch.

(2) Comment No. SUP020, Docket No. 75N–0183, Dockets Management Branch.

(3) Comment No. OB0015, Docket No. 75N–0183, Dockets Management Branch.

(4) "Two Year Chronic Oral Toxicity Study With Fat 80' 023/A in Albino Rats," Comment No. C00109, Volume 1, Appendix E, and Comment No. C00139, Volumes 1 through 8, Docket No. 75N–0183, Dockets Management Branch.

(5) "Eighteen Month Carcinogenicity Study with Fat 80' 023/A in Albino Mice," Comment No. C00109, Volume 3, Appendix I, and Comment No. C00139, Volume 9, Docket No. 75N–0183, Dockets Management Branch.

(6) "Three Phase Reproduction Study Albino Rats and Rabbits, Bacteriostat CH 3565," Comment No. C00134, TAB 7, and Comment No. C00139, Volumes 10 through 11, Docket No. 75N–0183, Dockets Management Branch.

(7) Letter from W. E. Gilbertson, FDA, to R. Bernegger, Ciba-Geigy Corp., coded LET028/ANS, Docket No. 75N–0183, Dockets Management Branch.

(8) Memorandum of Meeting between FDA Staff and Representatives of Ciba-Geigy Corp., Comment No. MM0007, Docket No. 75N–0183, Dockets Management Branch.

(9) "FAT 80' 023 2-Year Oral Administration in Rats," Volumes XLI, XLII, and XLIII and "Determination of FAT 80' 023 in Blood and Tissue Samples Taken During a Two-Year Chronic Oral Toxicity/Oncogenicity Study in Albino Rats," Volume XLIV, Comment No. RPT002, Docket No. 75N–0183, Dockets Management Branch.

(10) Letter from W. E. Gilbertson, FDA, to R. Bernegger, Ciba-Geigy Corp., coded LET034, Docket No. 75N–0183, Dockets Management Branch.

(11) Comments No. MM0003 and C00157, Docket No. 75N–0183, Dockets Management Branch.

(12) Letter from A. E. Castillo, EPA, to W. E. Gilbertson, FDA, coded LET033, Docket No. 75N–0183, Dockets Management Branch.

N. Comments on Drug Combinations

49. Several comments objected to the agency's decision not to allow combinations of an antimicrobial ingredient and a nonantimicrobial active ingredient or ingredients. (See comment 44, 43 FR 1210 at 1217.) The comments requested that the monograph provide for combinations of an antimicrobial active ingredient with a nonantimicrobial active ingredient or ingredients provided that the combinations are "labeled for use solely for the concurrent symptoms indicated for the active ingredients." Some of the comments pointed out that such combinations were submitted to the Panel for review, e.g., a combination of chloroxylenol and petrolatum (39 FR 33103 at 33104). One comment contended that it was contradictory for the agency to reject the chloroxylenol-petrolatum combination and at the same time define a skin wound protectant in § 333.3(h) of the tentative final monograph as a product that provides both a physical and chemical barrier to infection of small, cleansed wounds, in as much as nonantimicrobial ingredients appear to be necessary to provide the physical barrier of a skin wound protectant. One comment specifically requested that the combination of a topical antimicrobial ingredient with a topical anesthetic ingredient be included in the monograph, stating that such a combination has long been recognized as an effective method of treatment. Another comment made a similar request regarding the combination of alcohol and a topical anesthetic ingredient.

The agency agrees with the comments that antimicrobial ingredients (including alcohol) to help prevent infection can be combined appropriately with nonantimicrobial ingredients to provide concurrent relief for symptoms of minor cuts, scrapes, or burns provided the combination product meets the requirements of § 330.10(a)(4)(iv) (21 CFR 330.10(a)(4)(iv)).

In the previous tentative final monograph, the agency stated that no combinations of antimicrobial and nonantimicrobial active ingredients "are known to exist" (43 FR 127). The agency's statement was based on the Panel's recommended criteria for combining antimicrobial and nonantimicrobial active ingredients and the Panel's recommendation that "if a skin antiseptic claim is made it must meet the requirement of the definition of a skin antiseptic" (39 FR 33103 at 33106). In accordance with the Panel's criteria, neither the Panel in its report nor the agency in the tentative final monograph recognized any Category I skin antiseptics; therefore, no Category I combinations of skin antiseptic and nonantimicrobial ingredients existed. However, because this tentative final monograph is proposing a new category for first-aid antiseptics instead of the category of skin antiseptics and because the definitions for these categories are different, the agency reviewed the submissions to the Antimicrobial Panel in light of the new definition and has determined that combinations containing first aid antiseptics with a topical anesthetic or with a skin protectant do exist. The agency has tentatively determined that these combinations provide rational concurrent therapy, have been previously marketed OTC, meet the requirements in § 330.10(a)(4)(iv), and can be generally recognized as safe and effective. Accordingly, the agency is including the combinations mentioned by the comment in this tentative final monograph.

The agency proposed in § 348.50(b)(2) of the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5868) the following indication for local anesthetics: "For the temporary relief of" (select one of the following: "pain," "itching," or "pain and itching") (which may be followed by: "associated with" (select one or more of the following) "minor burns," "sunburn," "minor cuts," "scrapes," "insect bites," or "minor skin irritation.")

The agency proposed in § 347.50(b)(1) of the tentative final monograph for OTC skin protectant drug products (48

FR 6820 at 6832) the following indication for skin protectants: "For the temporary protection of minor cuts, scrapes, burns, and sunburn." These indications are very similar to the indication for first aid antiseptics in § 333.50(b) of this proposed monograph. Nevertheless, it should be noted that first aid antiseptics are classified in Category I for safety based on labeling that they be indicated for use only on small areas of the body for a minor cut, scrape, or burn and that they have a warning not to apply over large areas of the body. Accordingly, those Category I claims for external analgesic drug products or skin protectant drug products that refer to conditions other than minor wounds, and particularly conditions likely to involve large areas of the body (e.g., sunburn), would be Category II for topical antiseptic-anesthetic and antiseptic-skin protectant combination drug products. Accordingly, the agency is proposing the following combinations as Category I in this tentative final monograph:

(1) Any single first aid antiseptic active ingredient identified in § 333.10 may be combined with any single skin protectant active ingredient identified in § 347.10 provided that the product is labeled according to § 333.60.

(2) Any single first aid antiseptic active ingredient identified in § 333.10 may be combined with any single external analgesic active ingredient identified in § 348.10(a) provided the product is labeled according to § 333.60.

The agency is proposing that these combinations bear the general antiseptic labeling indication that appears in § 333.50(b). In addition, the agency is proposing that these combinations can bear the following additional indications:

(1) Antiseptic-external analgesic combination: "First aid for the temporary relief of" (select one of the following: "pain," "discomfort," "pain or discomfort," or "pain and itching") "in minor cuts, scrapes, and burns."

(2) Antiseptic-skin protectant combination: "First aid for the temporary protection of minor cuts, scrapes, and burns."

50. One comment submitted animal, human, and in vitro studies to establish that a combination of 4.7 percent phenol and 10.8 percent camphor (camphorated phenol) in an oil-based vehicle is safe and effective as a first aid product and skin wound protectant (Refs. 1 and 2). (Camphorated phenol is FDA's preferred common name for complexes of camphor and phenol.) The comment stated that this combination was consistent with the Panel's statement that "when camphor is used with phenol in an oil formulation, the concentration of phenol should be no more than 5 percent" (43 FR 1210 at 1238). The comment further stated that "the clathrate complexing of the two ingredients alters the toxicity materially" and that this product has had a long history of safe use with minimal accidental ingestions. The comment concluded that, because of the product's packaging, there is practically no likelihood of mistaking it for mineral oil or castor oil, as has happened with camphorated oil products. The agency has evaluated the reports submitted by the comment (Refs. 1 and 2) and the data submitted to the Antimicrobial I Panel and has determined that camphorated phenol (containing 4.7 percent phenol and 10.8 percent camphor) is safe and effective for use by consumers as a first aid antiseptic.

In a separate rulemaking for OTC external analgesic drug products, the agency categorized the complex (which was described as a combination in that rulemaking) containing camphor and phenol as Category I for short-term use (i.e., 7 days) as an external analgesic, e.g., "for pain and itching of minor cuts and scrapes." The indication for this drug used as an "external analgesic" (48 FR 5852) is similar to the claims in this proposed first aid monograph.

In the external analgesic rulemaking, the agency proposed the following warning for phenol and phenol-containing products: "Do not apply over large areas of the body or bandage" (48 FR 5852 at 5869). This warning is similar to the warning for phenol proposed by the Antimicrobial I Panel (39 FR 33133) and the agency in the previous tentative final monograph (43 FR 1238): "Warning: Do not * * * cover the treated area with a bandage or dressings." There is also an existing required warning in § 369.20 for carbolic acid (phenol) preparations (more than 0.5 percent) for external use: "Warning—Use according to directions. Do not apply to large areas of the body. If applied to fingers or toes, do not bandage." As discussed in comment 25, the agency has included the warning "Do not use in the eyes or apply over large areas of the body," to the general warnings applicable to all first aid antiseptic drug products. Consistent with the external analgesic tentative final monograph and 21 CFR 369.20, the agency is also proposing a separate warning specific for phenol containing products: "Do not bandage."

As discussed in the external analgesic rulemaking, the agency has verified that the amount of free phenol is reduced when camphor and phenol are combined. The Antimicrobial I Panel stated that "when camphor is used with phenol in an oil formulation, the concentration of phenol should be no more than 5 percent" (39 FR 33103 at 33133). In reviewing data on camphor/phenol combinations, the Antimicrobial I Panel concluded that "The presence of camphor also retards the absorption of phenol after topical application. A 1-hour exposure of the rat tail to a 4.8 percent aqueous phenol solution resulted in the absorption of 71 mg of phenol; whereas, the presence of 10.9 percent camphor combined with 4.5 percent phenol resulted in the absorption of only 16 mg phenol * * *" (39 FR 33122).

The agency concluded in the previous tentative final monograph for OTC topical antimicrobial drug products that "the total concentration of phenol in powders and in aqueous, alcoholic or oil formulations be restricted to less than 1.5 percent. When camphor is used with phenol in an oil formulation, the concentration of phenol should be no more than 5 percent" (43 FR 1210 at 1238). The agency agrees with the comment that, based on the data, the antiseptic phenol combined with camphor can be safely used at a higher concentration than phenol used alone. To reduce the irritating potential of phenol when concentrations of 4.7 percent are used, camphor must be present in excess of that concentration. Accordingly, the agency is including camphorated phenol (containing 4.7 percent phenol combined in a complex with 10.8 percent camphor) in a light mineral oil, U.S.P. vehicle in this first aid antiseptic tentative final monograph.

The agency agrees with the comment that camphor/phenol combinations are unlikely to be mistaken for mineral oil or castor oil and that the adverse reaction information supports the safety of the combination.

References

(1) Comment No. SUP013, Docket No. 75N-0183, Dockets Management Branch.

(2) Comment No. C00116, Docket No. 75N-0183, Dockets Management Branch.

51. One comment from a manufacturer of products containing camphorated metacresol disagreed with the Category II classification of formulations containing more than 5 percent phenol or amyltricresols when used with camphor and with the Category III classification of products containing less than 5 percent phenol or amyltricresols when used with camphor (43 FR 1210 at 1238). The comment claimed that "the special safety and effectiveness of these products is based on the existence of a camphor-metacresol complex or one-phase solution, which acts to release

controlled quantities of 'free' metacresol at completely non-toxic levels." The comment stated that a large number and variety of studies had been conducted to demonstrate the safety, effectiveness, and chemical identity of the complex and that, even though the most modern techniques had not been used, the studies should not have been rejected by FDA. The comment submitted new data (Ref. 1) purporting to show that metacresol has a low toxicity compared with other cresols and phenol; that camphorated metacresol is an effective bactericide; and that the antiseptic action of cresols is not due to protein binding and consequently would not encourage continued release of "free" metacresol from the camphorated metacresol complex. Citing the long marketing history of these products, the comment stated that no adverse drug reactions have been reported. The comment argued that this absence of complaints is especially significant because the products are primarily marketed to doctors, nurses, and paramedics for professional use in industrial settings. These professionals are trained to observe and report adverse reactions, treat a limited clientele, and are in close communication with their pharmaceutical suppliers. The comment requested, for the above reasons, that products containing the combination of camphorated metacresol be reclassified into Category I for safety and effectiveness for use as a skin wound cleanser and skin wound protectant without restriction on the metacresol content.

The agency has evaluated the data and concludes that camphorated metacresol limited to a range of camphor 3 to 10.8 percent and metacresol 1 to 3.6 percent in a 3:1 ratio is safe and effective as a first aid antiseptic.

Subsequent to the previous tentative final monograph, the recommendations on camphorated metacresol made by the Advisory Review Panel on OTC Antimicrobial II Drug Products in conjunction with its review of OTC antifungal drug products were published in the Federal Register of March 23, 1982 (47 FR 12460 at 12536). That Panel reviewed cresol, the mixture of ortho, meta, and para cresol, and concluded that "Cresol is structurally and pharmacologically related to phenol and * * * is more active against bacteria than phenol and has a phenol coefficient of 2 to 3. The three chemical isomers of cresol (*m*-cresol, *o*-cresol, *p*-cresol) vary little in bactericidal properties" (47 FR 12536). The agency agrees with these findings.

In a separate rulemaking for OTC external analgesic drug products, the agency regarded metacresol as similar to phenol and categorized camphorated metacresol as Category I for short-term use (i.e., 7 days) as an external analgesic, e.g., for pain and itching of minor cuts and scrapes (48 FR 5852 at 5858). This external analgesic indication is similar to the claims in this proposed first aid monograph. As discussed in the external analgesic rulemaking (48 FR 5858), the agency has determined that metacresol behaves similarly to phenol with respect to bonding with camphor and therefore can be considered a "complex" and categorized as camphorated metacresol.

Based on the available information, which includes recognition of the combination of phenol and camphor as Category I, data showing that metacresol has the same toxicity as phenol or is less toxic, and the new data showing that metacresol bonds to camphor similarly to phenol, the agency has tentatively concluded that camphorated metacresol is Category I when prepared from camphor and metacresol combined in a 3-to-1 ratio not to exceed a concentration of 10.8 percent camphor. Based on a 3-to-1 ratio of camphor to metacresol with a limit of 10.8 percent camphor, the upper limit for metacresol is 3.6 percent. This 3-to-1 ratio results in reduced irritation. The agency is proposing a lower limit of 1 percent metacresol based on information on marketed products submitted by the comment.

In addition, the same warning, "Do not bandage," as discussed in comment 50 with regard to phenol/camphor, will apply to camphorated metacresol.

The comment did not provide sufficient data to establish general recognition of safety of a concentration of metacresol greater than 3.6 percent when this ingredient is combined with camphor. The studies submitted by the comment (Ref. 1) were very limited in scope and were inadequate to demonstrate the safety of higher concentrations. Most of the animal toxicity studies tested only one animal, observed the animal only for a short period of time, and did not include a detailed examination of the animal following drug application. The comment's statements about rate of release of metacresol are unsupported because the comment submitted no information on the quantity of metacresol released under the conditions of use. The comment also did not submit any data to support the safety of concentrations of camphor above 10.8 percent.

The marketing history information submitted in the comment does not provide proof of safety for camphor concentrations above 10.8 percent or metacresol concentrations above 3.6 percent. The safety of camphorated metacresol as a first aid antiseptic above 3.6 percent metacresol and 10.8 percent camphor has not been established.

Therefore, the agency proposes to classify camphorated metacresol (a complex consisting of camphor and metacresol combined in a ratio of 3 parts camphor to 1 part metacresol) at concentrations from 1 to 3.6 percent metacresol and from 3 to 10.8 percent camphor as Category I for use as a first aid antiseptic.

References

(1) Comment No. SUP035, Docket No. 75N-0183, Dockets Management Branch.

(2) Comment No. C00098, Docket No. 75N-0183, Dockets Management Branch.

52. One comment stated that the Panel did not review safety and effectiveness data submitted to it on mercufenol chloride (orthohydroxyphenylmercuric chloride) 0.1 percent and secondary amyltricresols 0.1 percent as single ingredients and in combination for use as a patient preoperative skin preparation, skin antiseptic, and skin wound protectant (Ref. 1). The comment added that the agency did not discuss these ingredients alone or in combination in the previous tentative final monograph.

The comment asserted that secondary amyltricresols, mentioned in the previous tentative final monograph under phenol (43 FR 1210 at 1238), are not equivalent to phenol because of chemical differences and differing antimicrobial properties, formulation concentrations, and patterns of use. The comment requested the agency to make decisions on the safety and effectiveness of this ingredient when used alone, or in combination, as a patient preoperative skin preparation, a skin antiseptic, or a skin wound protectant.

The agency has reviewed the submitted data and finds that they are insufficient to determine the safety and effectiveness of 0.1 percent mercufenol chloride and 0.1 percent secondary amyltricresols either singly or in combination for use as a first aid antiseptic. Another panel, the OTC Miscellaneous External Panel, reviewed data other than that provided in this comment and found mercufenol chloride to be safe for topical use at a 0.056-

percent concentration (47 FR 436 at 441). However, the available data are insufficient to establish the safety of this ingredient at 0.1 percent. Only safety data on animals were submitted by the comment (Ref. 1); in general, these studies were conducted on a very small number of animals, did not detail methodology, and did not adequately describe results (physical conditions of the animals). The submitted in vitro studies also lack sufficient detail to establish the effectiveness of mercufenol chloride.

Secondary amyltricresols are mixtures of isomeric secondary amyltricresols, which are derivatives of phenol, and have pharmacological properties similar to phenol. The agency agrees with the comment that the mixture of secondary amyltricresols is not equivalent to phenol and should be categorized separately from phenol. The submitted safety data included a study by Broom (Ref. 2), who reported that amylmetacresol is relatively nontoxic and less toxic than hexylresorcinol in rats and mice.

No toxicity studies in humans were included in the information provided by the comment. However, in the tentative final monograph for OTC external analgesic drug products, published in the **Federal Register** of February 8, 1983 (48 FR 5852 at 5858), the agency proposed that metacresol up to a 3.6-percent concentration be considered safe when combined with camphor and that a 3-to-1 ratio of camphor to metacresol reduces the irritating properties of metacresol. Although cresols may cause some irritation when applied to minor wounds, the agency believes that secondary amyltricresols at the concentration requested (0.1 percent) would not present any safety concerns, particularly considering the short-term use of first aid products. The submitted data are, however, inadequate to establish the efficacy of secondary amyltricresols.

Data are also needed to determine the safety and effectiveness of the combination of mercufenol chloride and secondary amyltricresols. Only animal safety data are available, and these studies were limited to determinations of the minimum lethal dose by various routes of administration (Ref. 1). The submitted information on marketing history is not sufficient to provide general recognition of the safety of these ingredients. The data contained isolated reports of the combination of mercufenol chloride and secondary amyltricresols causing occasional skin irritation, such as burning and blistering (Ref. 1), adverse effects that need to be more fully studied.

Most of the effectiveness work on the combination of mercufenol chloride and secondary amyltricresols has been in vitro. The combination is reported to combine the antibacterial activity of the single ingredients, that is, mercufenol chloride, which is primarily active against gram-negative organisms, and secondary amyltricresols, which are primarily active against gram-positive organisms (Ref. 3). One in vivo study on the effectiveness of the combination as a patient preoperative skin preparation showed a substantial reduction in the skin microflora (Ref. 4). However, because neutralizers were not used, bactericidal activity cannot be differentiated from residual bacteriostatic activity. In addition, the effect of the 50-percent alcohol in the alcohol-acetone vehicle was not taken into consideration. Alcohol, 48 to 95 percent, has been classified Category I in this first aid antiseptic rulemaking.

Under the agency's guidelines for OTC drug combination products (Ref. 5), Category I active ingredients from the same therapeutic category that have different mechanisms of action may be combined to treat the same symptoms or condition if the combination meets the combination policy in all respects and the combination is on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose. Accordingly, both mercufenol chloride and secondary amyltricresols and the combination of these ingredients are placed in Category III. The combination needs further testing of the combined ingredients compared to each individual active ingredient to establish effectiveness of the combination as a topical antiseptic for first aid use.

References

(1) OTC Volume 020093.

(2) Broom, W.A., "A Note on the Toxicity of Amyl-meta-cresol," British Journal of Experimental Pathology, 12:327–331, 1931.

(3) Dunn, C.G., "Germicidal Properties of Phenolic Compounds," Industrial and Engineering Chemistry, 28:609–612, 1936.

(4) Maddock, W.G., and L.K. Georg, "Further Experience with Mercresin," American Journal of Surgery, 45:72–75, 1939.

(5) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

53. One comment submitted data on the safety and effectiveness of triclocarban and triclosan combined in a deodorant bar soap and requested that this antibacterial combination in a bar soap be included in the OTC topical antimicrobial final monograph (Ref. 1). The comment mentioned that these data were submitted prior to the publication of the previous tentative final monograph, but were not addressed in that document.

The data were not addressed in the previous tentative final monograph because they were received too late for inclusion in that document. As discussed in comment 26, deodorant bar soaps for which only cosmetic claims are made are considered cosmetics.

Reference

(1) Comments No. LET003 and SUP029, Docket No. 75N–0183, Dockets Management Branch.

54. One comment submitted data on the safety and effectiveness of a product containing a combination of eucalyptol, menthol, methyl salicylate, thymol, and 26.9 percent alcohol for use as a first aid remedy and topical antiseptic for the treatment of minor cuts and scratches (Ref. 1). Noting that the product is marketed primarily as an antiseptic mouthwash, the comment stated that it is also labeled and indicated for the treatment of minor cuts and scratches. The comment added that the safety of the ingredients and the total formulation had been acknowledged by two different FDA advisory panels, i.e., the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Panel (Cough-Cold Panel) and the Oral Cavity Panel.

References to antiseptic activity of the individual aromatic oils and their combination in the scientific literature were submitted (Ref. 1). Studies of the individual oils (eucalyptol, menthol, methyl salicylate, and thymol), their vapors, and solutions against a wide variety of gram-positive and gram-negative microorganisms were described in the comment. Phenol coefficients were reported for each of the oils. These coefficients show that each oil is more active than phenol against frequently occurring organisms. For example, the following approximate phenol coefficients have been reported: eucalyptol, 1.8; menthol, 5.1; methyl salicylate, 1.8; and thymol, 27.6 (Ref. 1).

The comment included studies (Ref. 1) to demonstrate that the combination of oils is more effective than each of the individual ingredients and that each of the oils provides a statistically significant contribution to the activity of the product.

Further support for the antiseptic activity of the combination is provided by the in vitro antiseptic activity test proposed by the OTC Oral Cavity Panel. The comment stated that at no time has the product failed to kill all three of the

prescribed microorganisms, *C. albicans, Streptococcus mutans,* and *Actinomyces viscosus,* in less than 5 minutes regardless of the test conditions. This includes tests conducted in the presence of saliva, horse serum, or fetal calf serum, each of which may inactivate certain antiseptic agents.

One submitted clinical study compared the antiseptic effect of the combination product, 70 percent ethanol, and water on the skin flora. The study revealed that a 60-second wash of the skin surface with the combination product results in a statistically significant reduction in numbers of surface bacteria. The comment pointed out that there were no significant differences between the combination product and 70 percent ethanol, a widely recognized and recommended antiseptic agent. A gradual recovery of the bacterial count occurs with time, but significantly reduced counts relative to pretreatment values exist 1 and 3 hours postwash after using the combination product and 70 percent ethanol.

Therefore, the comment requested that the agency consider this combination of ingredients to be Category I as a first aid antiseptic in the antimicrobial monograph.

Data and information on the individual essential oils were reviewed by the Oral Cavity Panel, and these ingredients were categorized as Category I for safety. (See the Federal Register of May 25, 1982, 47 FR 22760.) The agency affirms that Panel's conclusions that these individual essential oils are generally recognized as safe. The Cough-Cold Panel also reviewed the ingredients, except for methyl salicylate, and classified them in Category I for safety (41 FR 38311 at 38312). Methyl salicylate was classified in Category I for safety by the Topical Analgesic Panel (44 FR 69768); this classification was confirmed by the agency in the tentative final monograph for OTC external analgesic drug products (48 FR 5852).

The comment submitted data from in vitro studies showing that a formulation of 0.063 percent thymol, 0.042 percent menthol, 0.055 percent methyl salicylate, and 0.091 percent eucalyptol in 26.9 percent alcohol reduced the number of bacteria in *S. aureus* cultures 5.2 $\log_{10}$ within 1 minute at 37 °C when assayed at 40 percent of the formulation's recommended use concentration. Furthermore, when formulations lacking thymol, menthol, methyl salicylate, or eucalyptol were diluted and assayed as described above, the numbers of bacteria were reduced 0.6, 2.4, 3.1, and 3.4 $\log_{10}$, respectively, thus demonstrating that each essential oil contributed significantly to the total antimicrobial efficacy of the complete formulation. Because concentrations of alcohol exceeding 25 percent (v/v) are necessary to inactivate *S. aureus* within 1 hour (Ref. 2), concentrations of 10.76 percent (v/v), such as that contained in the diluted formulations assayed, would not be expected to have significant antimicrobial activity when tested as a single active ingredient. However, antiseptics prepared as hydroalcoholic tinctures have been demonstrated to be more efficacious than aqueous preparations even when dilutions of the tincture high enough to rule out the bactericidal action of the alcohol are assayed (Ref. 3). Thus, the addition of co-solvents to an aqueous phase can influence antimicrobial activity by either the inherent toxicity of the co-solvent, or through the effect of the co-solvent on the thermodynamic activity of an antimicrobial agent, or both (Ref. 4).

The comment also submitted data from in vivo studies which compared the antimicrobial efficacy of four treatment regimens: a formulation of the above mentioned essential oils in 26.9 percent alcohol; 70 percent (v/v) alcohol; water; and no treatment. Treatment consisted of wiping the skin surface for 1 minute with a 2"×2" sterile gauze sponge soaked in the treatment solution, or the site was left untreated to serve as the nontreated control. Bacterial samples were taken from the skin surface by a contact plate method once prior to treatment, immediately after treatment and again at 1 and 3 hours later. Results of the immediate post-treatment evaluation when compared with pre-treatment bacterial counts showed that 70 percent alcohol, the combination of essential oils in 26.9 percent alcohol, water, and no treatment reduced the numbers of organisms 1.69, 1.51, 0.43, and 0.03 $\log_{10}$, respectively. Statistically significant residual effects were observed at 1 and 3 hours after treatment with 70 percent alcohol and the combination of essential oils in alcohol, while water produced a significant reduction immediately and at 1 hour post-wash. Differences in antimicrobial efficacy between 70 percent alcohol and the combination of essential oils in alcohol at 0, 1, and 3 hours post-treatment were not statistically significant.

Although this combination product contains more than two active ingredients from the same pharmacological group (i.e., eucalyptol, menthol, methyl salicylate, and thymol), paragraph 3 of the agency's "General Guidelines for OTC Drug Combination Products" (Ref. 5) permits such a combination "* * * if the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingredients used alone at its therapeutic dose." In addition, although the individual ingredients have not been classified, the ingredients may be evaluated as a combination based on paragraph 5 of the agency's "General Guidelines" (Ref. 5), which states that "in some cases an ingredient may be appropriate for use only in a specific combination or data may be available only to support the use of the ingredient in combination but not as a single ingredient. In such cases the ingredient will be placed in Category I for use only in the permissible combinations and not as a single ingredient."

Based on these guidelines and discussion above, the agency believes that the combination of eucalyptol 0.091 percent, menthol 0.042 percent, methyl salicylate 0.055 percent, and thymol 0.063 percent in alcohol 26.9 percent may appropriately be included in this amended tentative final monograph as Category I for first aid antiseptic use.

References

(1) Comment No. C00135, Docket No. 75N-0183, Dockets Management Branch.

(2) Morton, H.E., "The Relationship of Concentrations and Germicidal Efficacy of Ethyl Alcohol," Annals of The New York Academy of Sciences, 53:191–196, 1950.

(3) Dunn, Cecil, G., "Germicidal Properties of Phenolic Compounds," Industrial and Engineering Chemistry, 28:609–612, 1936.

(4) Kostenbauder, H.B., "Physical Factors Influencing the Activity of Antimicrobial Agents," Disinfection, Sterilization and Preservation, Edited by Seymour S. Block, Lea and Febiger, Philadelphia, p. 913, 1977.

(5) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

55. One comment requested that the agency consider the combination of epinephrine hydrochloride 0.1 percent and methylbenzethonium chloride 0.25 percent for OTC use in the treatment of minor cuts and abrasions. The comment stated that this combination is rational because it contains an antimicrobial agent, methylbenzethonium chloride, to aid in controlling infections and a vasoconstrictor, epinephrine hydrochloride, to help stop the bleeding of a minor wound. The comment added that epinephrine hydrochloride has been marketed in combination products for 35 years; that its safety and efficacy have been confirmed by the Advisory Review Panel on OTC Hemorrhoidal Drug Products (Hemorrhoidal Panel); and that the agency had classified

methylbenzethonium chloride in Category I as a skin wound cleanser in the tentative final monograph for OTC topical antimicrobial products (43 FR 1210 at 1246).

The agency has reviewed the data submitted by the comment (Ref. 1) and concludes that the data are insufficient to establish the safety and effectiveness of a combination of epinephrine hydrochloride 0.1 percent and methylbenzethonium chloride 0.25 percent to treat minor cuts and scrapes.

As discussed in comment 45, the agency considers methylbenzethonium chloride to be safe and effective as a first aid antiseptic at concentrations of 0.13 to 0.5 percent. Although epinephrine has been used for many years as a vasoconstrictor and bronchodilator, its effect on a skin wound in an area of poor circulation, such as an elderly person's finger or toe, needs further study. It has been suggested that epinephrine should not be applied to an area supplied by end arteries, such as the finger, toe, or ear, because of the danger of vascular insufficiency and sloughing (Ref. 2). It should be determined whether vasoconstriction in such a compromised area could induce gangrene.

The agency also finds the submitted data inadequate to determine the effectiveness of this combination. Epinephrine has been used by injection for many years, particularly in local anesthetics to decrease bleeding during surgical procedures, but it has not been as extensively used topically to treat skin wounds. Most of the studies on human skin cited by the comment used either local or intramuscular injections of epinephrine, and not topical applications. No human skin wound studies using epinephrine to stop bleeding were cited by the comment. Further testing of the combination is necessary to determine its effectiveness as a first aid antiseptic for minor cuts and scrapes.

The agency's detailed comments and evaluations on the data and its recommendations for additional studies are on file in the Dockets Management Branch (Ref. 3).

References

(1) Comment No. C00149, Docket No. 75N-0183, Dockets Management Branch.

(2) Denton, J., R.L. Schreiner, and J. Pearson, "Circumcision Complication," Clinical Pediatrics. 17:285-6, 2978.

(3) Letter from W.E. Gilbertson, FDA to K. Johannes, Plough, Inc., coded LET040, Docket No. 75N-0183, Dockets Management Branch.

O. Comments on Testing

56. Several comments requested that the effectiveness requirements for the skin antiseptic drug product category be similar to the requirements for other antimicrobial categories, such as the patient preoperative skin preparation or surgical scrub, for which effectiveness data must show a reduction of the number of bacteria on the skin, and that studies for demonstrating prevention of overt skin infection not be required.

Several comments submitted protocols for determining the in vitro effectiveness of products for general antiseptic use. The lists of microorganisms to be tested varied; but *P. aeruginosa, S. aureus,* and *E. coli* were included in each protocol because they were considered to be the organisms commonly encountered.

One comment asked that efficacy data be reviewed in light of the relevancy of percentage limits of antiseptic to the label claim and that a minimum limit of antiseptic be established for microbiocidal effectiveness. The comment provided experimental data and described a protocol used to determine the quantitative antimicrobial activity of two products of 10 percent povidone-iodine solution. The protocol specified the test organisms for the microbial suspension and the neutralizer to be used and provided for the addition of organic matter (serum) to the culture media in order to determine the minimal inhibitory concentration of the products at different intervals (i.e., zero hour, 15 seconds, 30 seconds, 1 minute, and 5 minutes). Incubation temperature for this in vitro test was 35 °C.

OTC first aid antiseptic drug products are not intended for the treatment of infection or for the prevention of overt infection, but only as an aid in helping to prevent infection of minor cuts, burns, and scrapes. Therefore, the agency finds that studies demonstrating prevention of overt skin infection, which was included in the previous tentative final monograph as part of the definition for a "skin antiseptic," are not necessary for a first aid antiseptic labeled "to help prevent infection in minor cuts, scrapes, and burns."

Demonstrated in vitro antiseptic bactericidal or bacteriostatic action is of predictive value in projecting in vivo efficacy for first aid antiseptics. Based on the comments and the considerations above, the agency has developed effectiveness criteria and procedures for testing final formulations of first aid antiseptic drug products. As recommended by the comments, the organisms *P. aeruginosa. S. aureus,* and *E. Coli* are identified as organisms to be tested. Neutralizers and culture media are discussed in the testing procedures, which are being proposed for inclusion in § 333.70 of the monograph and are described below.

The agency invites specific comment at this time on the testing requirements being proposed in § 333.70. After reviewing any submitted comments or data, the agency may revise the testing procedures prior to establishing a final monograph. The agency also recognizes that the test procedures may need to be revised periodically as newer techniques are developed and proven adequate.

Therefore, the agency is proposing that an OTC first aid antiseptic drug product in a form suitable for topical application meet the standards of the in vitro test included in § 333.70. Because the agency has received data on hydrogen peroxide topical solution, U.S.P., iodine tincture, U.S.P., and iodine topical solution, U.S.P., sufficient to support efficacy for these drug product formulations (see comments 36 and 39), these drug products, when formulated to meet U.S.P. specifications, are exempt from the in vitro testing procedure described in § 333.70.

57. Two comments requested that the agency clarify its position on final formulation testing of antimicrobial drug products because of apparent contradictions between the response to comment 7 (43 FR 1210 at 1211), statements appearing under the testing guidelines at 43 FR 1240, and the response to comment 90 (43 FR 1224).

The agency agrees that there were some contradictory statements in the previous tentative final rule regarding final formulation testing. The agency clarifies in this amended tentative final monograph that all final formulations are required to meet the specifications in the monograph. The agency has provided a test for effectiveness of OTC first aid antiseptics in § 333.70 of the tentative final monograph (as described in comment 56) to be followed by manufacturers for testing the final formulations of OTC first aid antiseptic drug products. The data are not required to be submitted to FDA by the manufacturer. The agency intends to use the testing procedures set forth in the final monograph for any necessary compliance testing of these products. Products that do not meet the specifications in § 333.70 when tested according to the testing procedures set forth in that section or otherwise approved through the petition process described in § 333.70(f) will be considered in violation of the final regulation.

58. Numerous comments addressed the agency's modifications in the Panel's proposed testing guidelines (43 FR 1239

to 1240), the agency's statements on final formulation testing (43 FR 1211, 1224, and 1240), and specific protocols for upgrading an antimicrobial ingredient from Category III to Category I (43 FR 1242 to 1246). Stating that the testing guidelines were unclear and pointing out inconsistencies between the guidelines and the agency's responses to comments at 43 FR 1211 and 1223 to 1227, a number of comments requested clarification or proposed modifications of a number of items in the guidelines.

Several comments requested specific information or submitted protocols for testing Category III ingredients. One comment requested that manufacturers be permitted to determine which protocol to follow to establish safety or effectiveness of an ingredient. A number of comments objected to the agency's consideration of the testing guidelines as final, and urged revisions in the guidelines for publication in the **Federal Register.**

The agency acknowledges that there were some inconsistencies in the testing guidelines for safety and effectiveness proposed in the previous tentative final rule. The agency does not consider the previous testing guidelines as final. The agency is proposing in this amended tentative final monograph a test for final formulations of first aid antiseptic drug products. (See comment 56 above.) Manufacturers may propose other appropriate testing procedures for inclusion in the monograph, and these will be evaluated by the agency upon request. Suggested safety and effectiveness testing procedures of Category III ingredients not in a final formulation are described in the previous tentative final monograph. (See 43 FR 1240.) Because the agency intends to use the testing procedures set forth in the final monograph (and proposed in § 333.70) for any necessary compliance testing of first aid antiseptic drug products covered by the monograph, manufacturers may also use these procedures to test a formulated product containing a Category III ingredient. The test results could be submitted to the agency as part of the information described in the previous tentative final monograph (43 FR 1240) to support the safety and effectiveness of these ingredients.

59. One comment argued that all requirements for preservative testing and data retention under proposed § 333.65 are outside the scope of the OTC drug review rulemaking procedure and should be deleted from the monograph. The comment pointed out that the agency stated in the tentative final monograph that the present framework of the OTC drug review does not permit a review of inactive ingredients, such as preservatives (43 FR 1218). The comment also stated that preservatives by definition are inactive ingredients (43 FR 1214) and as such are not covered by the monograph. Consequently, the comment concluded it is inconsistent with current policy to retain the requirements in § 333.65 of the monograph. The comment requested that all references to preservative testing be deleted from the monograph, especially because these requirements are already covered by the current good manufacturing practice regulations (21 CFR part 211).

Another comment stated that tests to determine the effectiveness of preservative concentration of antimicrobial ingredients are appropriate. However, this comment, as well as another comment, objected to the data retention requirement in proposed § 333.65(c), pointing out that such a requirement exceeds the agency's inspection authority under the act. The comment stated that "defining regulations for topical antimicrobial products cannot be used as a vehicle for expanding the scope of the statute."

Several comments objected to the definition of antimicrobial preservative under § 333.3(b) and requested that it be modified in the following areas: Limiting the preservative to the minimum effective concentration, the requirement for lack of contribution to the claimed drug effects of the product, and the reference to "inadvertently added microorganisms."

Several comments objected to the modifications of the testing procedures as detailed in § 333.65 (a) and (b) from those in the "U.S.P. Antimicrobial Preservative Effectiveness Test" (Ref. 1) and the "CTFA Preservative Test" (Ref. 2). Stating that various parts of these modifications were incongruous, unclear, and conflicting, the comments requested that the U.S.P. and CTFA tests be retained without modifications.

The agency agrees that preservatives are considered inactive ingredients and, upon further review, concludes that it is not necessary to include preservative testing in the tentative final monograph for antimicrobial drug products. However, preservative ingredients must meet the provisions of 21 CFR 330.1(e). The testing procedures detailed in the "U.S.P. Antimicrobial Preservative Effectiveness Test" (Refs. 1 and 3) and the "CTFA Preservative Test" (Ref. 2) are adequate. Therefore, previously proposed §§ 333.3(b) and 333.65 are not being included in this amended tentative final monograph. FDA encourages drug manufacturers to use the U.S.P. and CTFA tests to assure the adequacy of preservative systems in individual products. In view of this action, it is not necessary to respond to the other comments regarding preservative testing.

References

(1) "United States Pharmacopeia XIX," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 587, 1975.

(2) "Determination of Adequacy of Preservation of Cosmetic and Toiletry Formulations," CTFA Technical Guidelines, The Cosmetic, Toiletry and Fragrance Association, Inc., Washington, DC, 1983.

(3) "United States Pharmacopeia XXII—National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1478, 1989.

II. The Agency's Amended Tentative Final Monograph

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

1. Summary of Ingredient Categories

The agency has carefully reviewed the claimed active ingredients submitted to this administrative record (Docket No. 75N–0183) including the advance notice of proposed rulemaking (39 FR 33103) and previous tentative final rule (47 FR 1210) for OTC topical antimicrobial drug products, the advance notice of proposed rulemaking for OTC topical alcohol drug products (47 FR 22324), and the advance notice of proposed rulemaking for OTC topical mercury-containing drug products (47 FR 436). Based upon the proposed definition of a first aid antiseptic discussed in comment 13, the agency has made a tentative classification for first aid antiseptic active ingredients.

In arriving at these classifications, the agency has considered all the available data and information, including an assessment of currently marketed ingredients that are labeled or suggested for use as first aid antiseptics. The concentrations described are based upon submitted data. In each case the ingredient has been extensively marketed and used clinically.

Many of the ingredients included in the tabulation below are in Category II and Category III because of a lack of data on use as a first aid antiseptic. However, all the ingredients have been included, as a convenience to the reader. The agency specifically invites comment and additional data on these ingredients.

The agency published an advance notice of proposed rulemaking for mercury-containing drug products on

January 5, 1982 (47 FR 436). That notice, based upon the recommendations of the Miscellaneous External Panel, proposed to classify OTC mercury-containing drug products for topical antimicrobial use as not generally recognized as safe and effective and as being misbranded. The agency received no comments. The Panel classified the mercurial ingredients, as a group, in Category II; some for lack of safety, some for lack of efficacy, and others due to a lack of both safety and efficacy. However, the Miscellaneous External Panel required bactericidal effect for Category I classification as a topical antimicrobial. Based on the proposed definition of "first aid antiseptic," the agency concludes that ingredients having bactericidal and/or bacteriostatic effects are suitable for inclusion in Category I. The agency's criteria are consistent with the Antimicrobial Panel's definition of an antimicrobial (43 FR 1246), i.e., "A compound or substance that kills microorganisms or prevents or inhibits their growth and reproduction * * *," and with section 201(o) of the act (21 U.S.C. 321(o)), which states: "The representation of a drug, in its labeling, as an antiseptic shall be considered to be a representation that it is a germicide, except in the case of a drug purporting to be, or represented as, an antiseptic for inhibitory use as a wet dressing, ointment, dusting powder, or such other use as involves prolonged contact with the body."

Acceptable first aid antiseptic ingredients must be in appropriate product forms to maintain the necessary prolonged contact with the skin in order to sustain their bacteriostatic action. Adequate bacteriostatic action can be demonstrated through in vitro studies. However, data from in vivo studies, such as the ones described for these products in the previous tentative final monograph (43 FR 1210 at 1242), would also be required for these ingredients to be classified in Category I. In light of these changes, the agency has placed those mercurial ingredients with submitted data, which were formerly in Category II solely for efficacy reasons, into Category III and invites interested persons to comment. These mercurial ingredients include calomel, merbromin, phenylmercuric nitrate, and ortho-hydroxyphenylmercuric chloride (mercufenol chloride). "Mercufenol Chloride" is the established name for "ortho-hydroxyphenylmercuric chloride" as listed in the 1991 edition of the "USAN and the USP dictionary of drug names" (Ref. 1). Mercufenol chloride is also discussed in comment 52.

Reference

(1) "USAN and the USP dictionary of drug names," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 369, 992, s.v. "Mercufenol Chloride."

Poloxamer 188 was included in the previous tentative final monograph as a "skin wound cleanser" (43 FR 1246); but, because this antimicrobial rulemaking contains only ingredients with antimicrobial activity and because poloxamer 188 has no such activity, it is not included in the updated tentative final monograph. Poloxamer 188 may be used as an inactive ingredient or pharmaceutical aid in OTC antimicrobial drug products.

The following list is included as a summary of the categorization of first aid antiseptic active ingredients proposed by the agency.

SUMMARY OF ANTIMICROBIAL ACTIVE INGREDIENTS [1]

Category I
Ingredients generally recognized as safe and effective for OTC first aid use within the established concentration(s)
Single ingredients
Alcohol 48 to 95 percent [2]
Benzalkonium chloride 0.1 to 0.13 percent
Benzethonium chloride 0.1 to 0.2 percent
Hexylresorcinol 0.1 percent
Hydrogen peroxide topical solution U.S.P. [4]
Iodine tincture U.S.P.
Iodine topical solution U.S.P.
Isopropyl alcohol 50 to 91.3 percent [2]
Methylbenzethonium chloride 0.13 to 0.5 percent
Phenol 0.5 to 1.5 percent
Combinations
Eucalyptol 0.091 percent, menthol 0.042 percent, methyl salicylate 0.055 percent, and thymol 0.063 percent in 26.9 percent alcohol [4]
Complexes
Camphorated metacresol (3 to 10.8 percent camphor and 1 to 3.6 percent metacresol) in a ratio of 3:1 [4]
Camphorated phenol (10.8 percent camphor and 4.7 percent phenol) in a light mineral oil, U.S.P. vehicle [4]
Povidone-iodine complex 5 to 10 percent
Category II
Ingredients not generally recognized as safe for OTC first aid use
Single ingredients
Ammoniated mercury [3]
Cloflucarban
Fluorosalan
Mercuric chloride (Mercury chloride) [3]
Mercuric oxide, yellow [3]
Mercuric salicylate [3]
Mercuric sulfide, red [3]
Mercury [3]
Mercury oleate [3]
Mercury sulfide [3]
Nitromersol [3]
Para-chloromercuriphenol [3]
Thimerosal [3]
Tribromsalan
Vitromersol [3]
Zyloxin [3]
Combinations and/or Complexes
None
Category III
Ingredients for which the available data are insufficient to make a final determination for OTC first aid use [1]
Single Ingredients
Benzyl alcohol [2]
Calomel (mercurous chloride) [3]
Chlorobutanol [2]
Chloroxylenol
Merbromin [3]
Mercufenol chloride (ortho-hydroxyphenylmercuric chloride, ortho-chloromercuriphenol) [3]
Phenylmercuric nitrate [3]
Secondary amyltricresols [4]
Triclocarban
Triclosan
Combinations and/or Complexes
Iodine complex (ammonium ether sulfate and polyoxyethylene sorbitan monolaurate) [4]
Iodine complex (phosphate ester of alkylaryloxy polyoxyethylene glycol)
Mercufenol chloride and secondary amyltricresols [4]
Nonylphenoxypoly (ethyleneoxy) ethanoliodine
Poloxamer-iodine complex
Triple dye
Undecoylium chloride iodine complex

[1] All ingredients (unless otherwise noted) in Antimicrobial I Drug Products Advance Notice of Proposed Rulemaking (39 FR 33103) and Tentative Final Monograph (47 FR 1210).
[2] Alcohol Drug Products, Advance Notice of Proposed Rulemaking (47 FR 22324).
[3] Mercury-Containing Drug Products, Advance Notice of Proposed Rulemaking (47 FR 436).
[4] Not previously reviewed, but categorized in the amended Tentative Final Monograph.

2. Testing of Category II and Category III Conditions

Recommended testing procedures for evaluating the effectiveness of the complete formulation of a first aid antiseptic drug product are included in proposed § 333.70. Suggested effectiveness testing procedures for active ingredients not in a final formulation and suggested safety testing are described in the previous tentative final monograph (see 43 FR 1210 at 1240 to 1242).

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any topical antiseptic 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 and in the Agency's Previous Recommendations

FDA has considered the comments and other relevant information and is amending the previous tentative final monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. The agency is proposing to amend the regulations for topical antimicrobial drug products for OTC human use by adding Subpart A—First Aid Antiseptic Drug Products to 21 CFR part 333 and by amending § 369.20 (21 CFR 369.20). A summary of the changes made by the agency in this amended tentative final monograph follows.

The agency is proposing that skin wound cleansers and skin wound protectants that contain active antimicrobial ingredients be deleted as separate drug product categories and be included in a new category identified as "first aid antiseptics." (See comment 13.) Ingredients that were classified Category I as skin wound cleansers have been classified in Category I as first aid antiseptics. These are benzalkonium chloride, benzethonium chloride, methyl benzethonium chloride, and hexylresorcinol.

2. The agency is proposing that the drug product category "skin antiseptic" be deleted as a separate category and be included in the drug product category identified as "first aid antiseptics." (See comment 13.)

3. A new statement of identity is proposed for the product categories of skin wound protectants, skin wound cleansers, and skin antiseptics. Products previously in those categories are to be identified as "first aid antiseptics." (See comment 9.)

4. The agency is including the following indication for first aid antiseptics: "First aid to help" (select one of the following: "Prevent," ("decrease" ("the risk of" or "the chance of")), ("reduce" ("the risk of" or "the chance of")), "guard against," or "protect against") (select one of the following: "Infection," "bacterial contamination," or "skin infection") "in minor cuts, scrapes, and burns." (See comment 16.)

Because OTC first aid antiseptics are used for the first aid treatment of minor cuts, scrapes, and burns, as are OTC first aid antibiotics, the agency believes that the indications for these two categories of drugs should be similar. The labeling being proposed for first aid antiseptics in this tentative final monograph, where appropriate, is consistent with the labeling adopted in the final monograph for OTC first aid antibiotic drug products (52 FR 47312). (See 21 CFR 333.150(b).)

With the inclusion of alcohol drug products in this rulemaking, labeling recommended for those products has also been incorporated into the first aid antiseptic labeling proposed in new § 333.50. (See comments 27, 28, 32, and 33.)

5. The agency is proposing the following definition for first aid antiseptics consistent with the indication for that drug product category: "An antiseptic-containing drug product applied topically to the skin to help prevent infection in minor cuts, scrapes, and burns." (See comment 13.)

6. The agency is proposing that skin wound cleansers and skin wound protectants without active antimicrobial ingredients do not fall within the scope of the antimicrobial rulemaking. (See comment 14.) Poloxamer 188 was included in the previous tentative final monograph as a "skin wound cleanser," but is not included in the updated tentative final monograph. This antimicrobial rulemaking will only contain ingredients with antimicrobial activity; poloxamer 188 has no such activity. This will not preclude the use of poloxamer 188 as an inactive ingredient or pharmaceutical aid in OTC antimicrobial drug products.

7. Proposed in vitro testing procedures for testing final formulations for use as first aid antiseptics are included in proposed § 333.70. The results need not be submitted to the agency. However, the agency intends to use these testing procedures for any necessary compliance testing. (See comment 57.)

8. The agency proposes to reclassify several ingredients that were placed in Category III either as skin wound cleansers, skin wound protectants, or skin antiseptics to Category I as first aid antiseptics. These ingredients are iodine (tincture and solution) and phenol (0.5 to 1.5 percent). (See comment 37 on iodine.) Phenol is being reclassified into Category I as a first aid antiseptic because the agency has reevaluated effectiveness data available to the agency from the literature and submissions to the Panel (OTC Volumes 020041, 020042, and 020043) which show that phenol (0.5 percent to 1.5 percent without limitation to its vehicle) meets the proposed effectiveness criteria provided in the definition of a first aid antiseptic.

9. The agency proposes to reclassify povidone-iodine complex and camphorated phenol from Category III as skin antiseptics to Category I as first aid antiseptics. (See comments 38 and 39 on povidone-iodine complex and comment 50 on camphorated phenol.)

10. The agency has placed several ingredients that were not reviewed in the previous tentative final monograph into Category I as first aid antiseptics based on data contained in comments to the previous tentative final monograph and information from other sources. These ingredients are hydrogen peroxide, camphorated metacresol (3 to 10.8 percent camphor and 1 to 3.6 percent metacresol in a ratio of 3 to 1), and a combination product containing eucalyptol 0.091 percent, menthol 0.042 percent, methyl salicylate 0.055 percent, and thymol 0.063 percent in 26.9 percent alcohol. Because chlorhexidine gluconate has never been marketed for use as a first aid antiseptic, it is not being included in the first aid antiseptic rulemaking. (See comments 34 on chlorhexidine gluconate, 36 on hydrogen peroxide, 51 on camphorated metacresol, and 54 on the combination product.)

11. Soaps containing antimicrobial ingredients are considered cosmetics when deodorancy or other cosmetic claims are the only claims made for the product. Deodorant labeling claims for antimicrobial soaps are not included in the amended tentative final monograph. (See comment 10.) Antimicrobial soap as a separate drug product category for first aid use is not being included in the amended tentative final monograph. The use of soaps containing antimicrobial ingredients and labeled for other uses, e.g., health care personnel hand washes, will be discussed in the segment of this rulemaking dealing with uses other than first aid in a future issue of the **Federal Register**. (See comments 10 and 19.)

12. Based upon the proposed definition of a first aid antiseptic, the agency has revised the labeling to eliminate several indications that were Category I in the previous tentative final monograph. These include "prevents skin infection," "controls infection," "degerming," "kills germs," "bacteriostatic," "bactericidal," "reduces the risk of infection and cross-infection," and "microbiocidal." (See comment 16.)

13. The directions for use are being revised to delete the phrase "after gentle washing with soap and water" because

alkaline soap may be inappropriate for use on damaged tissue. (See comment 20.)

14. The warnings in § 333.92(c)(4) "do not bandage tightly" and in § 333.99(c), which stated "the warning 'Do not use solution with occlusive dressing' may be used instead of the warning 'do not bandage tightly,' " which were proposed for all skin wound cleansers, are not being required for all first aid antiseptic drug products. This includes products containing benzalkonium chloride, benzethonium chloride, and methylbenzethonium chloride. The need for such warnings will be separately evaluated for each ingredient based on the ingredient's sensitizing and irritation potential. (See comment 22.)

15. The warning "Do not bandage" is being required for camphorated metacresol, camphorated phenol, and phenol. (See comments 50 and 51.)

16. The agency proposes to revise the warning "This product is not for use on wild or domestic animal bites. If you have an animal bite, consult your physician immediately." Rather than having the separate warning for animal bites, the agency is proposing to add the term "animal bites" to the warning that lists other conditions that need medical attention. The revised warning is as follows: "In case of deep or puncture wounds, animal bites, or serious burns, consult a doctor." (See comment 23.)

17. The agency proposes to revise and consolidate the warnings for skin wound cleansers, skin wound protectants, and skin antiseptics regarding the length of time these products can be used before consulting a physician. The previous tentative final monograph allowed 10 days of self-medication before consulting a physician. This amended tentative final monograph proposes 7 days for consistency with rulemakings for other topical products. The warning is also being revised so that it does not imply that these products are recommended to treat infection. The warning in § 333.93(c)(5) of the previous tentative final monograph that attempted to describe symptoms of infection to alert consumers when to consult a physician has been included in the new general warning in the amended tentative final monograph. The following warning replaces the separate warnings for the three drug products categories and is proposed for all first aid antiseptics, including alcohol: "Stop use and consult a doctor if the condition persists or gets worse. Do not use longer than 1 week unless directed by a doctor." (See comment 24.)

18. The agency is eliminating several redundant or unnecessary warnings proposed in the previous tentative final monograph. The proposed warning in § 333.93(c)(7), "Do not use on chronic skin conditions such as leg ulcers, diaper rash, or hand eczema," has been deleted because the 1-week use limitation warning and the indication should be sufficient to inform the consumer that first aid antiseptics are not to be used on longstanding skin conditions. The proposed warning in § 333.93(c)(6), "Do not use in the eyes," has been expanded to include "or apply over large areas of the body," which is consistent with the first aid antibiotic tentative final monograph. (See comment 25.)

19. The agency proposes to revise the statement of identity for alcohol drug products proposed by the Miscellaneous External Panel in § 333.98(a) as "alcohol for topical antimicrobial use" to the same statement of identity as other first aid antiseptics, i.e., "first aid antiseptic." (See comment 27.)

20. The agency proposes to delete the warning proposed by the Miscellaneous External Panel in § 333.98(c)(2) for products containing isopropyl alcohol, "Use only in a well-ventilated area; fumes may be toxic." (See comment 32.)

21. The advance notice of proposed rulemaking for alcohol drug products for OTC topical antimicrobial use is being adopted by the agency with changes for clarity, and is being incorporated into this amended tentative final monograph. The lower limit of ethyl alcohol is being reduced to 48 percent because of evidence that 48 percent ethyl alcohol is effective as a first aid antiseptic. (See comment 33.) The indications for alcohol and isopropyl alcohol are being modified for consistency with the other Category I first aid antiseptic ingredients. (See comment 33.)

22. The agency is proposing to change the minimum concentration of povidone-iodine for effectiveness from 7.5 percent to 5 percent because of data from studies on a marketed product showing effectiveness at the lower concentrations. (See comment 39.)

23. The agency is eliminating the requirement that iodophors carry a 2-year expiration date. (See comment 40.)

24. The agency is reclassifying povidone-iodine for first aid antiseptic use to Category I. (See comments 41 and 42.)

25. The agency is proposing to change the upper limit of the concentration for methylbenzethonium chloride to 1:200 (0.5 percent). (See comment 45.) In addition, the agency is proposing to change the upper limit for benthezonium chloride to 1:500 (0.2 percent) based on the recommendation of the Miscellaneous External Panel in its report on OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis, published in the **Federal Register** of December 3, 1982 (47 FR 54646).

26. The agency is removing the proposed restriction that dosage forms of triclosan be formulated only in a bar soap. (See comment 48.)

27. The agency is proposing to allow the combination of a Category I antimicrobial ingredient with a Category I analgesic, anesthetic, or antipruritic ingredient or with a Category I skin protectant ingredient. Therefore, new § 333.20 is being proposed in this amended tentative final monograph to include these combinations. (See comment 49.)

28. The agency is not including previously proposed §§ 333.3(b) and 333.65 in the amended tentative final monograph. Nevertheless, the agency encourages manufacturers to continue to test preservatives according to USP and CTFA tests to assure the adequacy of preservative systems in individual products. (See comment 59.)

29. The term "scrapes" has been substituted for the term "abrasions" in the labeling of the amended tentative final monograph for first aid antiseptics, which is consistent with the first aid antibiotic monograph.

30. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This amended tentative final monograph proposes that option. (See § 330.50(e).)

31. Several mercury-containing OTC topical antimicrobials have been reclassified from Category II to Category III for effectiveness. Mercurial ingredients placed in Category II for safety are not being reclassified. The ingredients being reclassified are calomel, merbromin, mercufenol chloride, and phenylmercuric nitrate. (See Part II. A.1.—Summary of Ingredient Categories.) This change is being made in keeping with the revised effectiveness criteria for the drug product category "first aid antiseptic" (see comment 56), which were not available at the time the Miscellaneous External Panel evaluated the effectiveness of mercurial ingredients.

32. The agency is proposing to remove a portion of § 369.20 applicable to OTC first aid antiseptic drug products when the final monograph eventually becomes effective because this portion of the regulations will be superseded by the final monograph (part 333, subpart A; proposed in the **Federal Register** of July 9, 1982 (47 FR 29986)). The item proposed for removal is the entry for "ANTISEPTICS FOR EXTERNAL USE" in § 369.20.

The agency recognizes that there are other portions of §§ 369.20 and 369.21 applicable to OTC first aid antiseptic drug products that will also be removed eventually, but not necessarily at the time the first aid antiseptic final monograph becomes effective. These items include the entries for "CARBOLIC ACID (PHENOL) PREPARATIONS (MORE THAN 0.5 PERCENT) FOR EXTERNAL USE," "CREOSOTE, CRESOLS, GUAIACOL, AND SIMILAR SUBSTANCES IN PREPARATIONS FOR EXTERNAL USE," and "MERCURY PREPARATIONS FOR EXTERNAL USE" in § 369.20 and the entry for "ALCOHOL RUBBING COMPOUND" in § 369.21. These entries are also applicable to other OTC drug rulemakings and will not be removed until all the applicable rulemakings become final.

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 first aid antiseptic 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 first aid antiseptic 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 invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC first aid antiseptic drug products. Types of impact may include, but are not limited to, costs associated with product testing, relabeling, repackaging, or reformulating. Comments regarding the impact of this rulemaking on OTC first aid antiseptic drug products should be accompanied by appropriate documentation. Because the agency has not previously invited specific comment on the economic impact of the OTC drug review on first aid antiseptic drug products, a period of 180 days from the date of publication of this proposed rulemaking in the **Federal Register** will be provided for comments on this subject to be developed and submitted. 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 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.

Interested persons may, on or before January 21, 1992, submit to the Dockets Management Branch 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 January 21, 1992. 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 July 22, 1992, 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 September 22, 1992. 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 (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 September 22, 1992. 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

21 CFR Part 333

Labeling, Over-the-counter drugs, Topical antimicrobial drug products.

21 CFR Part 369

Labeling, Medical devices, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act, it is proposed that subchapter D of chapter I of title 21 of the Code of Federal Regulations be amended in parts 333 and 369 as follows:

PART 333—TOPICAL ANTIMICROBIAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 333 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. New subpart A, consisting of §§ 333.1 through 333.70, is added to read as follows:

Subpart A—First Aid Antiseptic Drug Products

Sec.

Sec.
333.20 Permitted combinations of active ingredients.
333.50 Labeling of first aid antiseptic drug products.
333.60 Labeling of permitted combinations of active ingredients.
333.70 Testing of first aid antiseptic drug products.

Subpart A—First Aid Antiseptic Drug Products

§ 333.1 Scope.

(a) An over-the-counter first aid antiseptic drug product in a form suitable for topical administration is generally recognized as safe and effective and is not misbranded if it meets each condition in this subpart and each general condition established in § 330.1 of this chapter.

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

§ 333.3 Definitions.

As used in this subpart:

(a) *Antiseptic drug.* In accordance with section 201(o) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(o)), "The representation of a drug, in its labeling, as an antiseptic shall be considered to be a representation that it is a germicide, except in the case of a drug purporting to be, or represented as, an antiseptic for inhibitory use as a wet dressing, ointment, dusting powder, or such other use as involves prolonged contact with the body."

(b) *First aid antiseptic.* An antiseptic-containing drug product applied topically to the skin to help prevent infection in minor cuts, scrapes, and burns.

§ 333.10 First aid antiseptic active ingredients.

The active ingredient of the product consists of any of the following within the specified concentration established for each ingredient, and the product is labeled according to §§ 333.50 or 333.60:

(a) Alcohol 48 to 95 percent by volume in an aqueous solution denatured according to Bureau of Alcohol, Tobacco and Firearms regulations in 27 CFR part 20.

(b) Alcohol 26.9 percent when combined in accordance with § 333.20(c).

(c) Benzalkonium chloride 0.1 to 0.13 percent.

(d) Benzethonium chloride 0.1 to 0.2 percent.

(e) Camphorated metacresol (camphor 3 to 10.8 percent and metacresol 1 to 3.6 percent in a ratio of 3 parts camphor to 1 part metacresol).

(f) Camphorated phenol (camphor 10.8 percent and phenol 4.7 percent) in a light mineral oil, U.S.P. vehicle.

(g) Eucalyptol 0.091 percent when combined in accordance with § 333.20(c).

(h) Hexylresorcinol 0.1 percent.

(i) Hydrogen peroxide topical solution U.S.P.

(j) Iodine tincture U.S.P.

(k) Iodine topical solution U.S.P.

(l) Isopropyl alcohol 50 to 91.3 percent by volume in an aqueous solution.

(m) Menthol 0.042 percent when combined in accordance with § 333.20(c).

(n) Methylbenzethonium chloride 0.13 to 0.5 percent.

(o) Methyl salicylate 0.055 percent when combined in accordance with § 333.20(c).

(p) Phenol 0.5 to 1.5 percent.

(q) Povidone-iodine 5 to 10 percent.

(r) Thymol 0.063 percent when combined in accordance with § 333.20(c).

§ 333.20 Permitted combinations of active ingredients.

(a) Any single first aid antiseptic active ingredient identified in § 333.10 may be combined with any single external analgesic active ingredient identified in § 348.10(a) of this chapter provided the product is labeled according to § 333.60.

(b) Any single first aid antiseptic active ingredient identified in § 333.10 may be combined with any single skin protectant active ingredient identified in § 347.10 of this chapter provided the product is labeled according to § 333.60.

(c) The ingredients identified in § 333.10 (b), (g), (m), (o), and (r) may be combined provided the product is labeled according to § 333.60.

§ 333.50 Labeling of first aid antiseptic 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 "first aid antiseptic."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "First aid to help" (select one of the following: "prevent," ("decrease" ("the risk of" or "the chance of")), ("reduce" ("the risk of" or "the chance of")), "guard against," or "protect against") (select one of the following: "infection," "bacterial contamination," or "skin infection") "in minor cuts, scrapes, and burns." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (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) *For products containing any ingredient identified in § 333.10.* (i) "For external use only. Do not use in the eyes or apply over large areas of the body. In case of deep or puncture wounds, animal bites, or serious burns, consult a doctor."

(ii) "Stop use and consult a doctor if the condition persists or gets worse. Do not use longer than 1 week unless directed by a doctor."

(2) *For products containing any ingredient identified in § 333.10 (a) and (l).* "Flammable, keep away from fire or flame."

(3) *For products containing any ingredient identified in § 333.10 (e), (f), and (p).* "Do not bandage."

(d) *Directions.* The labeling of the product contains the following statements under the heading "Directions":

(1) "Clean the affected area."

(2) *For products that are ointments, creams, and liquids.* "Apply a small amount of this product on the area 1 to 3 times daily."

(3) *For products labeled for use as a wet compress.* "Bandage lightly. Keep bandage wet with solution."

(4) *For products packaged as sprays.* "Spray a small amount of this product on the area 1 to 3 times daily."

(5) *For products containing any ingredient identified in § 330.10 (a), (b), (c), (d), (g), (h), (i), (j), (k), (l), (m), (n), (o), (q), and (r) of this chapter.* "May be covered with a sterile bandage."

(6) *For products packaged as liquids or sprays.* "If bandaged, let dry first."

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

§ 333.60 Labeling of permitted combinations of active ingredients.

Statements of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the

product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable over-the-counter (OTC) drug monographs. For a combination drug product that does not have an established name, the labeling of the product states the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(b) *Indications.* The labeling of the product states, under the heading "Indications," the indication(s) for each ingredient in the combination, as established in the indications sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this paragraph, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (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.

(1) *For permitted combinations identified in § 333.20(a).* In addition to the required indication identified in § 333.50, the labeling of the product may state, under the heading "Indications," the following additional indication: "First aid for the temporary relief of" (select one of the following: "pain," "discomfort," "pain or discomfort," or "pain and itching") "in minor cuts, scrapes, and burns."

(2) *For permitted combinations identified in § 333.20(b).* In addition to the required indication identified in § 333.50, the labeling of the product may state, under the heading "Indications," the following additional indication: "First aid for the temporary protection of minor cuts, scrapes, and burns."

(3) *For permitted combinations identified in § 333.20(c).* The indications in § 333.50 should be used.

(c) *Warnings.* The labeling of the product states, under the heading "Warnings," the warning(s) for each ingredient in the combination, as established in the warnings sections of the applicable OTC drug monographs.

(d) *Directions.* The labeling of the product states, under the heading "Directions," directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated below. When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product:

(1) May not contain any dosage that exceeds those established for any individual ingredient in the applicable OTC drug monograph(s), and

(2) May not provide for use by any age group lower than the highest minimum age limit established for any individual ingredient.

§ 333.70 Testing of first aid antiseptic drug products.

A first aid antiseptic drug product in a form suitable for topical application will be recognized as effective if it contains an active ingredient included in § 333.10 and if at its lowest recommended use concentration it decreases the number of bacteria per milliliter in *Staphylococcus aureus* (ATCC No. 6538), *Escherichia coli* (ATCC No. 8739), and *Pseudomonas aeruginosa* (ATCC No. 9027) cultures (available from American Type Culture Collection (ATCC), 12301 Parklawn Dr., Rockville, MD 20852) by 3 $\log_{10}$ within 10 minutes at 32 °C in the presence of 10 percent serum in vitro. Drugs identified in § 333.10 (j), (k), and (l) are exempt from this testing procedure. Furthermore, an antiseptic drug product for inhibitory use as a wet dressing, ointment, dusting powder, or such other use involving prolonged contact with the body, will be recognized as effective if its active ingredient is included in § 333.10 and if a 1:120 dilution of the formulated drug product in growth medium without neutralizers prevents an increase in the number of organisms from an inoculum of 10^8 organisms of the above cultures when incubated at 32 °C for 48 hours. First aid antiseptic drug products that are not exempt from this provision must meet the specified requirements when tested in accordance with the following procedures unless a modification is approved as specified in paragraph (e) of this section.

(a) *Laboratory facilities, equipment, and reagents*—(1) *Laboratory facilities.* To prevent the contamination of test microorganism cultures with extraneous microorganisms, perform the test using aseptic techniques in an area as free from contamination as possible. Because test cultures of microorganisms may be adversely affected by exposure to ultraviolet light or chemicals in aerosols, do not test under direct exposure to ultraviolet light or in areas under aerosol treatment. Do environmental tests to assess the suitability of the testing environment frequently enough to assure the validity of test results.

(2) *Equipment.* Use laboratory equipment that is adequate for its intended use. Thoroughly cleanse the equipment after each use to remove any antiseptic residues. Keep the equipment covered when not in use. Sterilize clean glassware intended for holding and transferring the test organisms in a hot air oven at 200 to 220 °C for 2 hours. Use volumetric flasks, pipets, or accurately calibrated diluting devices when diluting standard and sample solutions. Use plastic or glass Petri dishes having dimensions of 20×100 millimeters. Use covers of suitable material.

(3) *Reagents*—(i) *Phenol stock solution.* Prepare a 5-percent weight to volume solution of phenol by the method described in the "Official Methods of Analysis of the Association of Official Analytical Chemists," Kenneth Helrich (ed.), 15th Ed., 1990, pp. 133–134, which is incorporated by reference in accordance with 5 U.S.C. 552(a) and 1 CFR Part 51. Copies are available from the Association of Official Analytical Chemists, 2200 Wilson Blvd., Suite 400, Arlington, VA 22201–3301, or available for inspection at the Office of the Federal Register, 1100 L St. NW., Washington, DC.

(ii) *Serum.* Use inactivated fetal bovine serum without added preservatives and/or anti-infective products.

(b) *Culture media and diluting fluids*—(1) *Ingredients.* Use Soybean-Casein Digest Medium for culture media and diluting fluids that conform to the standards prescribed by "The United States Pharmacopeia XXII/The National Formulary XVII." In lieu of preparing the media from the individual ingredients, the media may be made from dehydrated mixtures which, when reconstituted with distilled water, have the same or equivalent composition as media prepared from individual ingredients. Media prepared from dehydrated mixtures is to have growth-promoting, buffering, and oxygen tension-controlling properties equal to or better than media prepared from individual ingredients. Adjust the pH of each medium with 1 Normal hydrochloric acid or sodium hydroxide before sterilization, if necessary, so that after sterilization the pH will fall within the specified range prescribed by "The United States Pharmacopeia XXII/The National Formulary XVII." Steam sterilize the media in an autoclave at 121 °C for 20 minutes.

(2) *Neutralizers.* When neutralizers are added to culture media and diluting fluid, perform the following tests.

(i) *Neutralizer inactivation of antiseptic test.* Assay the neutralizer

efficacy for the test antiseptic as follows: Prewarm the test antiseptic, culture medium, test culture, and serum to 32 °C by incubating appropriate volumes of all solutions in a water bath at 32 °C for 5 minutes. Mix 0.8 milliliter of antiseptic (for controls use 0.8 milliliter of sterile water) with 9.0 milliliters of culture medium containing an appropriate antiseptic neutralizer followed by the addition of 0.2 milliliter of the test culture in 50 percent serum. Incubate the mixture of cells, serum, antiseptic, and neutralizer at 32 °C for 10 minutes. Remove aliquots, dilute, and assay for surviving bacteria by the plate-count assay method using diluting and plating media containing appropriate neutralizers, if required. Results obtained showing differences greater than 20 percent between test and control cultures indicate that the neutralizer used to inactivate the test antiseptic is ineffective. Reject results obtained from tests employing ineffective neutralization procedures.

(ii) *Neutralizer effect on bacteria viability test.* Test the effect of neutralizers used to inactivate antiseptic active ingredients on cell viability by diluting aliquots of each test organism culture in Medium A (without neutralizer), specified in paragraph (b)(3)(i) of this section, and in the appropriate diluting fluid (neutralizing medium), specified in paragraph (b)(4) of this section. Determine the number of bacteria in aliquots of appropriate dilutions by the plate-count assay method utilizing growth agar medium containing the same neutralizer concentration as the diluting medium. Determine neutralizer effects on cell viability by comparing the relative number of microorganisms growing on Medium B, specified in paragraph (b)(3)(ii) of this section, with and without added neutralizers. Results obtained showing differences greater than 20 percent between cultures diluted in medium with and without neutralizers indicate that, at the concentration utilized, the antiseptic neutralizer alters the determination of viable cells in the test cultures. Reject results obtained from tests in which the neutralizer employed alters the determination of viable cell numbers.

(3) *Culture media*—(i) *Medium A (without neutralizers).* Use soybean-casein digest fluid medium corresponding to that described in paragraph (b) of this section.

(ii) *Medium B.* Soybean-casein digest agar medium. Same as Medium A, except for the addition of 15 grams of agar per liter.

(iii) *Medium C.* Same as diluting fluid 1, except for the addition of 15 grams of agar per liter.

(iv) *Medium D.* Same as diluting fluid 2, except for the addition of 15 grams of agar per liter.

(v) *Medium E.* Same as diluting fluid 3, except for the addition of 15 grams of agar per liter.

(4) *Diluting fluids*—(i) *Diluting fluid 1.* Diluting medium for neutralizing quaternary ammonium and phenolic antiseptic ingredients. Same as Medium A, except for the addition of 5 grams of lecithin and 40 milliliters of polysorbate 20 per liter.

(ii) *Diluting fluid 2.* Diluting medium for neutralizing iodophor antiseptic ingredients. Same as Medium A, except for the addition of 5 grams of sodium thiosulfate per liter.

(iii) *Diluting fluid 3.* Diluting medium for neutralizing mercurial antiseptic ingredients. Same as Medium A, except for the addition of 1 gram of sodium thioglycollate and 2.5 grams of sodium bisulfite per liter.

(c) *Test organisms.* (1) Use cultures of the following microorganisms:

(i) *Staphylococcus aureus* (ATCC No. 6538).

(ii) *Pseudomonas aeruginosa* (ATCC No. 9027).

(iii) *Escherichia coli* (ATCC No. 8739).

(2) *Preparation of suspension.* Maintain stock cultures on Medium B agar slants by monthly transfers. Alternatively, cultures may be lyophylized and stored at −70 °C. Incubate new stock transfers 2 days at 32 °C; then store at 2 to 5 °C. From stock culture, inoculate tubes of Medium A and make at least 4 but less than 30 consecutive daily transfers in Medium A, incubating at 32 °C, before using the culture for testing. Use a 22- to 26-hour culture of organisms grown in Medium A at 32 °C for the test.

(3) *Determination of cell number in broth cultures.* Prepare serial 1:10 dilutions of each culture in Medium A and determine the number of cells per milliliter of culture by the plate-count assay method. Do not use cultures stored at 4 °C for more than 48 hours for assay. Do not use cultures containing less than 10^9 cells per milliliter.

(4) *Plate-count assay.* For each culture to be assayed, pipet 1 milliliter of each prepared dilution into each of two sterile Petri plates. To each plate, add 20 milliliters of sterile Medium B that has been melted and cooled to 45 °C (if neutralizers are required, use the corresponding agar growth medium with the appropriate neutralizer). Mix the sample with the agar by tilting and rotating the plate and allow the contents to solidify at room temperature. Invert the Petri plates and incubate at 32 °C for 48 hours. Following incubation, count the number of developing colonies. Use Petri plates containing between 30 and 300 colonies in calculating the number of bacteria per milliliter of original culture.

(5) *Test organism antiseptic resistance test.* To insure that antiseptic resistance properties of each organism have not altered substantially, determine the resistance to phenol at 20 °C for each organism as described in "Phenol Coefficient Methods" referenced in paragraph (a)(3) of this section.

(i) *Escherichia coli.* A culture of *Escherichia coli* (ATCC No. 8739) is satisfactory for test purposes if it has resistance to phenol at 20 °C at least as follows:

Phenol	5 min	10 min	5 min
1:90 dilution...	+ or 0	+ or 0	0
1:100 dilution.	+	+	+ or 0

(ii) *Pseudomonas aeruginosa.* A culture of *Pseudomonas aeruginosa* (ATCC No. 9027) is satisfactory for test purposes if it has resistance to phenol at 20 °C at least as follows:

Phenol	5 min	10 min	15 min
1:80 dilution...	+ or 0	+ or 0	0
1:90 dilution...	+	+	+

(iii) *Staphylococcus aureus.* A culture of *Staphylococcus aureus* (ATCC No. 6538) is satisfactory for test purposes if it has resistance to phenol at 20 °C at least as follows:

Phenol	5 min	10 min	15 min
1:60 dilution...	+ or 0	+ or 0	0
1:70 dilution...	+ or 0	+	+

(d) *Test procedures*—(1) *Method 1*—(i) *Method validation.* This test is valid only for those antiseptics that are water soluble and/or miscible and that can be neutralized by one of the subculture media specified in paragraphs (b)(3) and (b)(4) of this section or that can be overcome by dilution.

(ii) *Bactericidal assay procedure.* Prewarm all test solutions by incubating appropriate volumes at 32 °C in a water bath for 5 minutes. Pipet 1.0 milliliter of serum, 1.0 milliliter of appropriate bacterial test culture, and 8.0 milliliters of test antiseptic at its recommended use concentration into a medication tube and mix well. Incubate at 32 °C for 10

minutes. Remove triplicate 1-milliliter sample aliquots and dilute in Medium A containing appropriate neutralizers. Determine the number of surviving organisms per milliliter of test culture by the plate-count method using plating media containing appropriate neutralizers, if required.

(iii) *Bacteriostatic assay procedure.* Prewarm all test solutions by incubating appropriate volumes at 32 °C in a water bath for 5 minutes. Pipet 1.0 milliliter of serum, 1.0 milliliter of appropriate bacterial test culture and 8.0 milliliters of test antiseptic at its recommended use concentration into a medication tube and mix well. Pipet 1.0 milliliter aliquots of this test mixture into triplicate medication tubes containing 100 milliliters of Medium A without neutralizers and mix well. Incubate at 32 °C for 48 hours and determine the number of organisms per milliliter of culture by the plate-count method.

(2) [Reserved]

(e) *Test modifications.* The formulation or mode of administration of certain products may require modification of the testing procedures in this section. In addition, alternative assay methods (including automated procedures) employing the same basic chemistry or microbiology as the methods described in this section may be used. Any proposed modification or alternative assay method shall be submitted as a petition under the rules established in § 10.30 of this chapter. The petition should contain data to support the modification or data demonstrating that an alternative assay method provides results of equivalent accuracy. All information submitted will be subject to the disclosure rules in part 20 of this chapter.

PART 369—INTERPRETATIVE STATEMENTS RE WARNINGS ON DRUGS AND DEVICES FOR OVER-THE-COUNTER SALE

3. The authority citation for 21 CFR part 369 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 371).

§ 369.20 [Amended]

4. Section 369.20 *Drugs; recommended warning and caution statements* is amended in subpart B by removing the entry for "ANTISEPTICS FOR EXTERNAL USE."

Dated: May 20, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

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