DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 356

[Docket No. 81N–033A]

RIN 0905–AA06

Oral Health Care Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Oral 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 a tentative final monograph that would establish conditions under which over-the-counter (OTC) oral antiseptic drug products (drug products used to help decrease the chance of infection in wounds in the mouth) are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Oral Cavity Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by August 8, 1994. Because new testing procedures for OTC oral antiseptic drug products are included in this tentative final monograph, the agency is allowing a period of 180 days for comments and objections instead of the normal 60 days. New data by February 9, 1995. Comments on the new data by April 10, 1995. Written comments on the agency's economic impact determination by August 8, 1994.

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–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of May 25, 1982 (47 FR 22760), 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 oral health care drug products, together with the recommendations of the Advisory Review Panel on OTC Oral Cavity Drug Products (Oral Cavity 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 August 23, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by September 22, 1982. In the **Federal Register** of July 30, 1982 (47 FR 32953), in response to a request for an extension of time, the comment period and reply comment period for OTC oral health care drug products were extended to November 22, 1982 and December 22, 1982, respectively.

In the **Federal Register** of December 28, 1982 (47 FR 57739), the reply comment period was extended to January 21, 1983.

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

In response to the advance notice of proposed rulemaking, 11 drug manufacturers, 3 professional organizations, 4 health professionals, and 1 individual consumer submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above).

FDA is issuing the tentative final monograph for OTC oral health care drug products in several segments. This document is the third segment to be published, and it contains the agency's responses to comments on OTC oral antiseptic drug products and to comments on the drug or cosmetic status of certain oral antiseptic ingredients and claims. The first segment of the tentative final monograph covering OTC oral health care anesthetic/analgesic, astringent, debriding agent/oral wound cleanser, and demulcent drug products was published in the **Federal Register** of January 27, 1988 (53 FR 2436). The second segment, an amendment to the tentative final monograph to include OTC relief of oral discomfort drug products, was published in the **Federal Register** of September 24, 1991 (56 FR 48302). Another part of the OTC oral health care drug products rulemaking involves antiplaque and antiplaque-related products. The agency published a call-for-data for OTC antiplaque ingredients in the **Federal Register** of September 19, 1990 (55 FR 38560). The data received in response to that call-for-data are currently being evaluated by the Dental Products Panel. The Panel's recommendations to the agency regarding the safety and effectiveness of antiplaque and antiplaque-related drug products will be published in an advance notice of proposed rulemaking in a future issue of the **Federal Register**.

The advance notice of proposed rulemaking, which was published in the **Federal Register** on May 25, 1982 (47 FR 22760), 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 present document is designated as a "tentative final monograph." In this tentative final monograph (proposed rule) to amend part 356 (21 CFR part 356) (proposed in the **Federal Register** of January 27, 1988, 53 FR 2436), FDA states for the first time its position on the establishment of a monograph for OTC oral antiseptic drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC oral health care drug products and will include oral antiseptic drug products.

This proposal constitutes FDA's tentative adoption of the Oral Cavity Panel's conclusions and recommendations on OTC oral antiseptic drug products, as modified on the basis of the comments received and the agency's independent evaluation of that report. 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.

The OTC drug procedural regulations (21 CFR 330.10) provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA does not use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required)

at the final monograph stage. In place of Category I, the term "monograph conditions" is used; in place of Categories II or III, the term "nonmonograph conditions" is used. 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 oral health care drug products (47 FR 22760), the agency suggested that the conditions included in the monograph (Category I) be effective 6 months 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 6 months after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

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

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

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

In the event that new data submitted to the agency during the allotted 12-month comment and new data period are not sufficient to establish "monograph conditions" for OTC oral antiseptic drug products, the final rule will declare these products to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)), for which new drug applications approved under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 are required for marketing. That rule would also declare that in the absence of an approved new drug application, these products would be misbranded under section 502 of the act (21 U.S.C. 352). The rule will then be incorporated into 21 CFR part 310, subpart E—Requirements for Specific New Drugs or Devices, instead of into an OTC drug monograph in part 356.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the **Federal Registers** of January 30, 1973 (38 FR 2781) (dental drug products) and July 20, 1973 (38 FR 19444) (oral health care drug products) 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

A. General Comments on Oral Antiseptic Ingredients

1. Several comments objected to the recommendation of the majority of the Oral Cavity Panel that only one Category III indication is appropriate for oral antiseptics, i.e., for the treatment of sore mouth and sore throat. One comment contended that antiseptic mouthwashes are not intended to be used primarily in the treatment of sore mouth and sore throat. Two comments maintained that the Oral Cavity Panel's recommendations that antiseptic mouthwashes be used solely for this indication is inconsistent with the commonly accepted purpose of these products. Another comment stated that the use of oral antiseptics solely for the treatment of sore mouth or sore throat, as the Panel recommended, would result in a disservice to consumers by depriving them of safe, familiar products upon which they depend. A number of comments discussed the use of oral antiseptic ingredients to reduce dental plaque, gingivitis, or both.

The agency notes that the Oral Cavity Panel used the term "antimicrobial agent" to describe an ingredient that kills microorganisms or prevents or inhibits their growth and reproduction. In this tentative final monograph, in order to be consistent with terminology proposed in the tentative final monograph for OTC first aid antiseptic drug products in the **Federal Register** of July 22, 1991 (56 FR 33644), the agency is proposing to replace the Panel's term "antimicrobial" with the term "antiseptic."

The Oral Cavity Panel only reviewed antiseptic ingredients for sore mouth and sore throat claims and did not specifically evaluate the effectiveness of oral antiseptics to inhibit plaque formation. Although data on plaque reduction as a measure of the effectiveness of OTC oral antiseptics were presented to that Panel, it did not accept such data because it believed that "the rationality of plaque reduction as a criterion of effectiveness of antimicrobial agents for use in the mouth and throat is highly debatable, and evidence of the validity of the method is scant" (47 FR 22760 at 22840 to 22842). The Panel was not charged with reviewing drug products used to treat dental or periodontal diseases, and

it did not address ingredients with antiplaque claims.

Because no advisory review panel reviewed the safety and effectiveness data on particular ingredients, including oral antiseptics, for antiplaque or gingivitis indications, the agency announced a call-for-data for ingredients contained in products bearing antiplaque and antiplaque-related claims in the **Federal Register** of September 19, 1990 (55 FR 38560). A substantial amount of information has been submitted to the agency pursuant to that call-for-data. The safety and effectiveness data submitted to the agency for various antiplaque and antiplaque-related ingredients are currently being evaluated by the Dental Products Panel. That Panel will advise the Commissioner of Food and Drugs on the promulgation of a monograph establishing conditions under which oral antiseptic drugs for antiplaque and antiplaque-related use are generally recognized as safe and effective and not misbranded.

In the call-for-data, the agency stated that, in order to be eligible for review under the OTC drug review procedures, an ingredient must have been marketed in a product with the relevant indication to a material extent and for a material time (21 U.S.C. 321(p)(2)). The agency specifically requested information demonstrating such marketing. The marketing data submitted to the agency by various manufacturers includes data on ingredients marketed in the United States, as well as data on ingredients that have only been marketed in other countries. Agency policy currently requires ingredients to have been marketed in the United States as of a certain date (December 4, 1975) to be eligible for consideration in the OTC drug review. Because of the passage of time, some antiplaque ingredients have entered the marketplace since 1975 and have been marketed for a number of years. The agency is reevaluating its policy for eligibility in the OTC drug review in relation to the statutory language "used to a material extent and for a material time" within the meaning of 21 U.S.C. 321(p)(2). The agency is also reevaluating its longstanding policy that foreign marketing alone is not an adequate basis for an ingredient to be considered in the OTC drug review. The agency's conclusions on these matters will affect many other therapeutic categories of drugs in addition to antiplaque products. For example, the agency is currently reviewing petitions to include sunscreens and phytomedicines marketed only in Europe in the OTC drug review. The ultimate review status of some of the antiplaque ingredient(s) is dependent on the resolution of this broader policy, which will be discussed in a future issue of the **Federal Register**.

The agency agrees with the comments that more than one indication may be appropriate for oral antiseptics. Although the Oral Cavity Panel's recommended indication for temporary relief of sore throat and sore mouth remains in Category III in this tentative final monograph, the agency is proposing a Category I indication for oral antiseptics used to help in the prevention of infection in minor sore mouth conditions. The agency is also requesting additional data to support the Panel's recommended Category III indication. (For a further discussion regarding the indications for OTC oral antiseptic drug products, see section I.K., comment 22.)

2. Two comments maintained that the safety of oral antiseptics is well established. One of the comments noted that the Oral Cavity Panel had initially placed oral antiseptic active ingredients in Category I for safety, but after questions were raised about the carcinogenic, teratogenic, and mutagenic potential of these ingredients, the Panel placed them in Category III. Maintaining that the chemical nature and the extensive scientific history of oral antiseptics do not lead to the conclusion that these materials are carcinogenic, teratogenic, or mutagenic, the comment noted that the review of quaternary ammonia compounds written for the Panel by one of its members concludes that quaternary ammonia compounds are safe for use in the oral cavity. The comment also quoted the following from the tentative final monograph for OTC topical antimicrobial drug products published in the **Federal Register** of January 6, 1978 (43 FR 1210 at 1238 and 1239):

> The Commissioner disagrees with the Panel that carcinogenicity, mutagenicity, or teratogenicity studies must be completed. The Commissioner concludes that, in the absence of any data suggesting that * * * has any carcinogenic, mutagenic, or teratogenic potential, testing for these properties should not be required.

The comment contended that "the parallel with oral antiseptics is striking and conclusive."

Both comments disagreed with the Panel that long-term use of oral antiseptics could cause harmful shifts of the oral flora, arguing that no such effects have been reported for this class of products and the available evidence suggests that their occurrence is unlikely. As an example, one comment stated that fungal overgrowth leading to thrush (candidiasis or moniliasis) that is commonly associated with the administration of broad spectrum antibiotics is one type of floral shift that could be troublesome. However, the comment asserted that there is no basis for supposing that frequent or even abusive use of OTC antiseptic mouthwashes could lead to thrush because part of the testing procedure for active antiseptic ingredients has been an in vitro test showing effectiveness against the fungus *Candida albicans*, which is the organism principally responsible for thrush.

Regarding the Oral Cavity Panel's suggestion that antiseptic mouthwashes could selectively eliminate "beneficial" organisms from the mouth, opening the way to the adverse effects of pathogenic flora, the comment asserted that in "all the literature of the microbial etiology of oral disease there are no reports stating or implying such an adverse shift of oral flora." In support of this statement, the comment cited reviews by Socransky (Ref. 1) and Loesche (Ref. 2). The comment also cited a report by Volpe et al. (Ref. 3) that no harmful floral shift resulted when mouthwashes containing cetylpyridinium chloride, benzethonium chloride, or hexachlorophene were used.

The comment stated that members of the Nonprescription Drug Manufacturers Association (NDMA) Task Group (formerly known as The Proprietary Association Task Group) estimate that, over a period of 10 years, its companies have conducted studies of antiseptic mouthwashes involving over 5,000 subjects for intervals ranging from 1 week to 1 year. Professional supervision and examination have demonstrated no instances of adverse effects resulting from floral shifts. The comment asserted that this is conclusive evidence of the safety of oral antiseptics.

The comment noted that another example of an occasional and undesirable effect of the prolonged use of antibiotics is lingua nigra or black hairy tongue. Maintaining that this condition is associated with *Candida* and with members of the related genera, *Actinomyces*, *Nocardia*, and *Streptomyces*, the comment asserted that because in vitro testing of oral antiseptics by the NDMA Task Group included proof of effectiveness against *Actinomyces* as well as *Candida*, there is no reason to believe that black hairy tongue would result from any use of oral antiseptics.

The Oral Cavity Panel evaluated the adverse effects of antiseptic ingredients contained in oral health care drug products from the following two

standpoints: (1) Short-term use to treat sore mouth and sore throat and (2) long-term use for cleansing, elimination of mouth odors, and other purposes where no symptoms of a disease exist (47 FR 22760 at 22848). The Panel did not consider OTC oral health care drug products appropriate for prophylactic use to prevent the development of symptoms or disease states of the mouth and throat (47 FR 22778). It concluded that antiseptic ingredients should be used for oral health care only when specific symptoms (e.g., sore throat or sore mouth) are present to justify the need for a specific product whose effectiveness has been established (47 FR 22834).

Although the Oral Cavity Panel placed no oral antiseptics in Category I, it placed 25 antiseptic ingredients in Category III for effectiveness. Additionally, the Panel determined that 16 of those 25 ingredients are safe for short-term use in the oral cavity. It did not determine that any antiseptic ingredients are safe (i.e., Category I) for long-term use in the oral cavity. Ingredients considered by the Panel to be safe for short-term use as OTC antiseptics in the oral cavity (i.e., Category III for effectiveness and Category I for safety) include phenol, carbamide peroxide in anhydrous glycerin, ethyl alcohol, and hydrogen peroxide. Ingredients placed in Category III for safety and effectiveness by the Panel include cetylpyridinium chloride, domiphen bromide, and povidone-iodine. The Panel also recommended labeling for oral antiseptics in OTC oral health care drug products that includes a warning restricting use to not more than 2 days (47 FR 22850).

The Panel did not clearly distinguish between the use of oral antiseptic ingredients in mouthwashes (long-term) and oral first aid products (short-term). The agency believes that many of these ingredients were placed in Category III for safety by the Panel because the ingredients are used in mouthwashes that are recommended by manufacturers for long-term use on a daily basis. (For a discussion of the time limits for use of oral antiseptics, see section I.K., comment 25.) The agency believes that the Panel's concerns are not necessarily relevant to the short-term use of these ingredients (i.e., up to 7 days). For example, the Panel stated that "extensive clinical observations also indicate that PVP-I [povidone-iodine] is generally nonirritating and nonsensitizing when applied to the skin and mucous membranes" (47 FR 22760 at 22884) and that dequalinium chloride has a low degree of toxicity similar to other quaternary ammonia compounds (quats) (47 FR 22760 at 22867). Nevertheless, the Panel placed povidone-iodine and dequalinium chloride in Category III for safety. The Panel recognized the safety of the commercially available concentrations of domiphen bromide, but stated that because controlled studies had not been done on the effects of domiphen bromide when used on a long-term basis, its safety could not be assumed (47 FR 22868 and 22869).

Accordingly, the agency concludes that the assessment of short-term safety of oral antiseptics should be determined on an individual basis based upon customary use (see section I.E., comment 8; section I.G., comment 12; and section I.I., comment 15). The agency invites comment on the safety of specific ingredients for use on a short-term basis.

When OTC oral antiseptics are indicated for short-term use and there is an absence of data suggesting that the ingredients evaluated by the Oral Cavity Panel have any carcinogenic, mutagenic, or teratogenic activities, the agency agrees with the Panel that the sponsor of a product should not be expected to conduct studies to obtain data on their tumorigenicity, mutagenicity, or teratogenicity. Such studies are often conducted by the National Cancer Institute and other agencies when necessary. The agency notes that benzethonium chloride is currently being evaluated for carcinogenic potential in the National Toxicology Program (NTP). (See section I.C., comment 5.)

The safety of long-term daily usage of OTC oral antiseptic ingredients in the oral cavity will be evaluated by the Dental Products Panel as part of its safety and effectiveness review of OTC antiplaque ingredients and will be discussed in a subsequent segment of the rulemaking for OTC oral health care drug products, to be published in a future issue of the **Federal Register**. (See section I.A., comment 1.)

References

(1) Socransky, S. S., "Microbiology of Periodontal Disease—Present Status and Future Considerations," *Journal of Periodontology*, 48:497–504, 1977.

(2) Loesche, W. J., "Chemotherapy of Dental Plaque Infections," *Oral Sciences Review*, 9:65–107, 1976.

(3) Volpe, A. R. et al., "Antimicrobial Control of Bacterial Plaque and Calculus and the Effects of the Agents on Oral Flora," *Journal of Dental Research*, 48:832–841, 1969.

3. Several comments and two reply comments disagreed with the Oral Cavity Panel's recommendation that OTC oral health care drug products containing pharmacologically active concentrations of antimicrobial ingredients should not be used to achieve a cosmetic effect, such as a reduction of mouth odor (47 FR 22760 at 22844). The comments contended that the use of ingredients in cosmetic mouthwash products is outside the scope of the OTC drug review procedure, which is limited to drug actions and drug claims. Arguing that the Panel's recommendation advocates the position that the regulatory classification of a product is dependent solely on the ingredient it contains, the comments maintained that it is a well-established regulatory policy that the intended use of a product determines whether it is regulated as a drug or as a cosmetic and that the intended use is determined by the manufacturer's representations and labeling claims. The comments stated that claims for the reduction or suppression of mouth odor and for oral cavity cleansing or refreshing are cosmetic claims. To support their contentions, many of the comments cited the definitions of "drug" and "cosmetic" in sections 201(g) and 201(i) of the act (21 U.S.C. 321(g) and 321(i)), the legislative history of the act, and prior case law. Some comments also quoted the following statement delivered to the Oral Cavity Panel in 1974 by the then FDA chief counsel:

> Generally, a product label will be the determining factor as to how a product will be classified, i.e., a drug or cosmetic. The overall safety of a product will also be a major factor in such classification. For example: The claim "kills germs that cause odor," would be considered a cosmetic claim; the claim "kills germs that cause disease" would be considered a drug claim * * *. (Ref. 1)

Several comments stated that the agency has a long-standing policy that cosmetics containing antimicrobial ingredients or other pharmacologic agents are not drugs unless drug claims are made for them. Some of the comments pointed out that FDA's policy concerning drug versus cosmetic status has been stated in many documents, including the procedural regulations governing the OTC drug review (37 FR 9464 to 9475) and official trade correspondence, and that the policy was restated in the tentative final monograph for OTC antiperspirant drug products, published in the **Federal Register** of August 20, 1982 (47 FR 36492), and in the report of the Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products (Vaginal Panel), published in the **Federal Register** of October 13, 1983 (48 FR 46694). Many comments pointed out that in both the OTC antiperspirant

drug products rulemaking and the OTC topical antimicrobial drug products rulemaking, the FDA agreed that a product that contains antimicrobial ingredients to reduce microbial flora solely for the purpose of cleansing or reducing odor is a cosmetic and not a drug and that such cosmetic uses are outside the scope of OTC drug monographs. Concluding that the Oral Cavity Panel's recommendations are without legal foundation and are contrary to the provisions of the act and the legal precedents established for more than 40 years, the comments requested that FDA reject the Panel's recommendations and adhere to the traditional drug/cosmetic distinctions.

One comment stated that the Oral Cavity Panel appeared to base its proposal to delete all cosmetic indications for antimicrobial mouthwash products on the finding that topical antimicrobials as a class are unsafe and ineffective. Asserting that action to be contrary to the substantial scientific evidence presented to that Panel and to the Advisory Review Panels on OTC Topical Antimicrobial Drug Products (the Antimicrobial I and II Panels), the comment stated that antimicrobial ingredients, used appropriately, are no less safe than other ingredients commonly used as cosmetics. A reply comment added that there are extensive scientific data demonstrating the effectiveness of an antimicrobial mouthwash in suppressing mouth odor.

Another reply comment agreed with the Panel that cosmetic claims are not acceptable as "indications" for the OTC oral health care drug products rulemaking insofar as cosmetic claims are not drug indications. However, the reply comment stated that this should not preclude truthful and nonmisleading information about the cosmetic usefulness in the product's labeling and mentioned antidandruff shampoos and anticaries toothpastes as two examples of OTC products with both drug and cosmetic claims. The reply comment argued that dual claims should be permitted for an OTC oral health care drug product, e.g., that it refreshes or deodorizes the mouth (a cosmetic claim) and aids in the temporary relief of discomfort due to occasional sore throat or sore mouth (a drug claim), just as such dual claims are permitted for antidandruff shampoos, which are represented to clean hair (a cosmetic claim) and to prevent dandruff (a drug claim), and for anticaries toothpastes, which are represented to clean teeth and to prevent tooth decay.

The comments requested that the agency recognize the following phrases as cosmetic claims for OTC oral health care products and, therefore, consider them as outside the scope of the OTC drug review: "Kills germs that cause bad breath," "mouth refreshment," "clean feeling," "control of mouth odor," "control of bad breath," "an aid to the daily care of the mouth," and "causing the mouth to feel clean." Two comments argued that terms such as "antimicrobial," "antiseptic," "kills germs," "kills germs by millions on contact," "antibacterial," and other synonymous phrases can be properly used to describe cosmetic functions, i.e., cleansing or refreshing and deodorizing, without creating drug connotations. The comments stated that when used in connection with oral hygiene and deodorizing representations, such claims are cosmetic claims because the context in which they appear connotes cosmetic purposes only. These comments concluded that mouthwashes, rinses, and gargles labeled solely with traditional cosmetic claims for cleansing, refreshing, or deodorizing the mouth or breath are subject to regulation only as cosmetics and not as drugs.

The Oral Cavity Panel stated that claims for the suppression of mouth odor in the labeling of OTC antiseptic health care products are drug claims because they are linked to a drug action, i.e., antimicrobial activity (47 FR 22760 at 22844). Concluding that such claims "* * * indicate that a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect" (47 FR 22857), the Panel classified claims for the suppression of mouth odor as well as claims for the cleansing or freshening of the mouth in Category II.

The act provides the statutory definitions that differentiate a drug from a cosmetic. A "drug" is defined 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)(B) and 321(g)(1)(C)). A "cosmetic," on the other hand, is defined as an article intended to be "* * * 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 agency agrees with the comments that the intended use of a product is the primary determining factor as to whether it 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 Ass'n* v. *Mathews*, 557 F.2d 325, 334 (2d Cir. 1977).)

In determining whether a product is a drug or a cosmetic, the intended use may be established from the type and amount of ingredient(s) present, as well as the product's labeling. For example, in some instances, the mere presence of certain therapeutically active ingredients could make a product a drug even in the absence of drug claims. In these cases, the intended use would be implied because of the known or recognized drug effects of the ingredient (e.g., fluoride in a dentifrice). However, in other instances, the presence of an ingredient (e.g., an antimicrobial), in and of itself, does not make a product a drug when no drug claim is made.

The agency does not agree with the Panel that claims for the suppression of mouth odor in the labeling of an oral product containing an antiseptic ingredient necessarily makes that product a drug. Oral products that contain antiseptic ingredients are considered "cosmetics," and not "drugs," if only deodorant (or other cosmetic) claims are made for the products. The agency stated in the tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33648) 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. Claims such as "mouth refreshment," "clean feeling," "control of mouth odor," "control of bad breath," and "for causing the mouth to feel clean" are considered cosmetic claims in accordance with section 201(i) of the act and are not included in this tentative final monograph.

However, any broader claims that represent or suggest a therapeutic use for the product would subject it to regulation as a drug. For example, the agency considers the phrase "an aid to daily care of the mouth" to be a drug claim because it implies that the product exerts a therapeutic benefit. The agency also considers terms such as "antibacterial," "antimicrobial," "antiseptic," or "kills germs" in the labeling of oral products to imply that the product will have a therapeutic effect. The agency concludes that such statements would constitute a drug claim for the product because consumers would perceive the intended effect to be achieved by a drug action. Likewise, any of the cosmetic statements mentioned above could become part of a drug claim if additional statements are included. For example, cosmetic claims such as

"control of mouth odor" and "for causing the mouth to feel clean" become drug claims when therapeutic terms are added as follows: (1) "antimicrobial for control of mouth odor," or (2) "kills germs to help the mouth feel clean." Furthermore, use of the term "active ingredient(s)" in the labeling of these products would imply that the product possesses a drug-like property and, thus, would cause the product to be considered a drug.

Products marketed only as cosmetics are not subject to this rulemaking, but are subject to the provisions of sections 601 and 602 of the act (21 U.S.C. 361 and 362) relating to adulteration and misbranding of cosmetics. The final OTC drug monograph for these products will cover only the drug use of the active ingredients listed therein. The concentration range, limitations, warnings, and directions established for the ingredients in the monograph may not apply to the use of the same ingredients in products intended solely as cosmetics. However, some of these factors may be considered by the agency in determining the safety of an ingredient for cosmetic uses. Those products intended for both drug and cosmetic use will be required to conform to the requirements of the final monograph. However, such products, in addition to bearing the indications allowed for OTC oral health care drug products, may also be labeled for cosmetic uses, such as deodorancy or cleansing, in conformity with section 602 of the act and the provisions of 21 CFR parts 701 and 740.

In accordance with the revised labeling requirements for OTC drug products, it is the agency's view that cosmetic claims may not appear within the boxed area designated "APPROVED USES." As discussed in the final rule on the agency's "exclusivity policy" (51 FR 16258 at 16264 (paragraph 14)), cosmetic terminology is not reviewed and approved by FDA in the OTC drug monographs and therefore could not be placed in the box. Cosmetic claims may appear elsewhere in the labeling, should manufacturers choose the labeling alternative provided in § 330.1(c)(2)(i) or (c)(2)(iii) for labeling drug/cosmetic products. Although the agency does not specifically prohibit commingled drug and cosmetic labeling in other than the indications section, such claims should be appropriately described so that consumers will more readily be able to differentiate the drug aspects from the cosmetic aspects of such labeling. If commingled drug and cosmetic labeling claims are confusing or misleading, the product's labeling could be misleading within the meaning of the act and misbranded under sections 502(a) and 602(a) of the act (21 U.S.C. 352(a) and 362(a)).

Reference

(1) Summary Minutes of the Advisory Review Panel on OTC Oral Health Care Drug Products, June 13 and 14, 1974, OTC Vol. 130PA2, Dockets Management Branch.

B. Comment on Alcohol

4. One comment expressed confusion regarding the Oral Cavity Panel's discussion and conclusions on ethyl alcohol (47 FR 22760 at 22871 to 22873). As an example, the comment mentioned that the Panel considered ethyl alcohol to be safe for use in the oral cavity while also stating that "Ethyl alcohol above 20 percent is considered to be an irritant * * *." Pointing out that the Panel also mentioned 70 percent alcohol (47 FR 22873), the comment questioned if it was permissible to use 70 percent alcohol as a solvent. The comment also wondered how the Panel determined that "The quantity [of alcohol] absorbed from the mouth and throat is not significant," (47 FR 22872). The comment concluded that, because it appears that the Panel's report lacks sufficient proof of safety and effectiveness of alcohol in concentrations over 20 percent and because of the high vulnerability of elderly people and children to alcohol, oral health care products containing more than 20 percent alcohol should not be permitted to stay on the market.

The agency reviewed the Oral Cavity Panel's discussion regarding ethyl alcohol (alcohol) as an active ingredient in OTC oral health care drug products and did not find any statement concerning alcohol above 20 percent being considered an irritant. However, in a report on OTC agents for the relief of oral discomfort published concurrently with the Oral Cavity Panel's report in the **Federal Register** of May 25, 1982 (47 FR 22712), the Dental Panel stated that alcohol above 20 percent is an irritant to the dental pulp and, therefore, concentrations above 20 percent should not be used in agents for the relief of toothache in an open tooth cavity (47 FR 22712 at 22726).

The Oral Cavity Panel concluded that alcohol is safe for use as an OTC oral antimicrobial ingredient (47 FR 22760 at 22872). However, the Panel did not clearly define a safe concentration of alcohol. The Panel also stated that commercially available mouthwashes contain alcohol as a solvent in concentrations up to 35 percent, but that concentrations above 35 percent cause burning of the mucous membranes (47 FR 22872). The Panel specifically stated that concentrations of alcohol that kill bacteria, e.g., 70 percent alcohol, cause burning and intense discomfort and are too irritating when applied to inflammations of the mucous membranes of the oral cavity (47 FR 22873). For the above reasons and because alcohol has a marked potential for abuse, the Panel recommended that the quantity of alcohol used as a solvent in pharmaceutical preparations should be limited to 35 percent.

In its report on OTC agents for the relief of oral discomfort (47 FR 22712 at 22737), the Dental Panel accepted the safety of 1.5 percent phenol in 70 percent alcohol for direct application to the gums for up to 7 days. That Panel concluded that up to 70 percent alcohol was an appropriate vehicle for 5 to 20 percent benzocaine with a maximum dosage of 1 milliliter (mL) and that compound benzoin tincture (74 to 80 percent alcohol) and benzoin tincture (75 to 83 percent alcohol) were safe for occasional application to small areas of the oral mucosa regardless of the high alcohol content (47 FR 22746).

The Oral Cavity Panel considered alcohol ineffective as an antimicrobial ingredient at concentrations below 70 percent (47 FR 22872 to 22873). However, that Panel also postulated that the lower concentrations of alcohol used as a solvent for an antimicrobial ingredient could act synergistically with the antimicrobial ingredient to produce an enhanced antimicrobial effect. The Panel concluded that there were insufficient data from controlled studies to establish the effectiveness of alcohol alone as an antiseptic ingredient for the treatment of symptoms such as sore mouth and sore throat, and the Panel placed it in Category III.

In the advance notice of proposed rulemaking for OTC alcohol drug products for topical antimicrobial use (47 FR 22324), the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel) stated that the "irritant action of alcohols is particularly marked on mucosa. The more concentrated the alcohol, the more pronounced are its irritant effects." That Panel recommended caution in the topical use of 60 to 95 percent alcohol and 50 to 91.3 percent isopropyl alcohol on the mucous membranes (47 FR 22324 at 22327) and placed the indication "For application to mucous membranes" in Category II (47 FR 22332). In the tentative final monograph for OTC first aid antiseptic drug products, the agency discussed this indication and stated that the use of alcohol on the mucous membranes of the mouth and throat would be addressed in the rulemaking

for OTC oral health care drug products (56 FR 33644 at 33656).

The agency is aware of a recent study (Ref. 1) indicating that men and women using mouthwashes with 25 percent or higher alcohol content on a regular long-term basis have a slightly increased risk of oral and pharyngeal cancers. Moreover, the risk rose with longer and more frequent mouthwash use. After adjusting for tobacco and alcohol consumption, men had a 40-percent higher risk and women had a 60-percent higher risk of these cancers, compared to those who did not use a mouthwash product. Although these findings do not firmly establish the risk relationship between use of an alcohol-containing mouthwash product and these cancers, they show a need to look further at this relationship. The agency is also aware of three earlier studies demonstrating an apparent association between long-term mouthwash use and an increased risk of oral and pharyngeal cancers (Refs. 2, 3, and 4). Although these studies may have no bearing on the safety of the short-term use of drug products containing alcohol, the agency believes that serious consideration must be given to the results of these studies to determine whether there is a need to limit the amount of alcohol permitted in oral health care drug products.

In 1992, the agency sent letters to two manufacturers' associations requesting data and information on the relationship between alcohol-containing drug products and oral and pharyngeal cancers and the extent of alcohol in OTC oral health care drug products (Refs. 5 and 6). In response, the associations jointly submitted a list of OTC mouthwashes, their alcohol content, and their 1990 sales data (Ref. 7), a reanalysis (Ref. 8) of the study on the association between the use of alcohol-containing mouthwashes and oral/pharyngeal cancer (Ref. 1) discussed previously, and a review (Ref. 8) of related medical and scientific literature pertaining to the etiology of oral cancer. The agency is currently evaluating the data and information submitted.

The agency notes that alcohol is used as a solvent in many OTC oral health care drug products currently on the market. When alcohol is included in oral antiseptic products, the agency believes that the amount of alcohol absorbed from topical application of the product to the mouth and throat to be insignificant. Such products are usually formulated as mouthwashes (oral rinses) or gargles and are retained in the mouth for a short period of time (usually 1 minute or less) and then spit out, or are applied as very small amounts of the product to discreet areas of the oral mucosa. However, the agency believes that alcohol should be included in OTC oral health care drug products only if the alcohol is necessary to dissolve the active ingredient(s).

The agency is currently evaluating the use of alcohol in all OTC drug products. On December 17, 1992 (Ref. 9), the OTC Drugs Advisory Committee discussed the use of alcohol in OTC drug products for oral ingestion and recommended to the agency that such products should not contain more than the minimum amount of alcohol needed as a solvent for the active ingredient, for preservative purposes, or for taste enhancement. The Committee specifically recommended the following:

1. For persons 12 years of age and above, a maximum alcohol concentration up to and including 10 percent volume-to-volume;

2. For children age 6 to under 12, a maximum alcohol concentration up to and including 5 percent volume-to-volume; and

3. For children under 6 years of age, a maximum alcohol concentration up to and including 0.5 percent volume-to-volume.

Based on the Committee's recommendations, the agency published a proposed rule on OTC drug products intended for oral ingestion that contain alcohol in the **Federal Register** of October 21, 1993 (58 FR 54466). That proposal would establish a maximum concentration limit for alcohol as an inactive ingredient in OTC drug products intended for oral ingestion.

In conclusion, the agency is evaluating the use of alcohol in all OTC drug products, is investigating a possible link between the regular use of alcohol-containing mouthwashes and oral and pharyngeal cancers, and is considering limiting the amount of alcohol permitted in such products. Although the agency is not proposing in this tentative final monograph to limit the amount of alcohol used as a solvent in OTC oral health care drug products, it urges all manufacturers to limit the alcohol content of all OTC drug products to the smallest amount compatible with the dissolution of the active ingredient(s).

References

(1) Blot, W. J. et al., "Mouthwash Use and Oral Conditions in the Risk of Oral and Pharyngeal Cancer," *Cancer Research*, 51:3044–3047, 1991.

(2) Wynder, E. L. et al., "Oral Cancer and Mouthwash Use," *Journal of the National Cancer Institute*, 70:255–260, 1983.

(3) Blot, W. J., D. M. Winn, and J. F. Fraumeni, "Oral Cancer and Mouthwash," *Journal of the National Cancer Institute*, 70:251–253, 1983.

(4) Weaver, A., S. M. Fleming, and D. B. Smith, "Mouthwash and Oral Cancer: Carcinogen or Coincidence?" *Journal of Oral Surgery*, 37:250–253, 1979.

(5) Letter from W. E. Gilbertson, FDA, to E. E. Kavanaugh, Cosmetic, Toiletry and Fragrance Association, coded LET 17, Docket No. 81N–0033, Dockets Management Branch.

(6) Letter from W. E. Gilbertson, FDA, to J. D. Cope, Nonprescription Drug Manufacturers Association (NDMA) coded LET 16, Docket No. 81N–0033, Dockets Management Branch.

(7)Comment No. LET25, Docket No. 81N–0033, Dockets Management Branch.

(8) Comment No. 53, Docket No. 81N–0033, Dockets Management Branch.

(9) Summary Minutes of the Nonprescription Drugs Advisory Committee Meeting, December 16 and 17, 1992, OTC Vol. 13CTFM.

C. Comment on Benzethonium Chloride

5. One comment disagreed with the Oral Cavity Panel's classification of benzethonium chloride in Category III for safety. The comment criticized the Panel's statement that "Adequate data on absorption and attainment of toxic blood levels and the metabolic fate of quats [quaternary ammonium compounds] are not available" (47 FR 22760 at 22860). The comment contended that information on the absorption of benzethonium chloride is available and that submissions to the Panel (Refs. 1 and 2) contained extensive data on the absorption and distribution of benzethonium chloride in chickens and in pregnant rats and their fetuses.

The comment also objected to the Oral Cavity Panel's statement that "No data are available on the mutagenic, tumorigenic, or teratogenic effects of benzethonium chloride when used in mouthrinses or gargles for long-term use on a daily basis for oral health care" (47 FR 22860). The comment contended that five studies submitted to the Panel (Refs. 3 through 7) show that tumorigenicity and teratogenicity of benzethonium chloride are not a problem. The comment mentioned several other studies that were available to the Panel and supposedly further substantiate that benzethonium chloride is not a teratogen and does not impede fertility or adversely affect postnatal survival of pups (Refs. 8 through 12).

The comment pointed out that the Oral Cavity Panel made several comments in its discussion of benzalkonium chloride (47 FR 22760 at 22858 to 22860) indicating concerns similar to those raised regarding benzethonium chloride, but the Panel still placed benzalkonium chloride in Category I for safety. The comment

stated that it could not understand how the Panel could conclude that benzalkonium chloride is safe while concluding that benzethonium chloride is not safe, when the supporting data for benzalkonium chloride were not as extensive. Adding that 88 million units of a mouthrinse containing benzethonium chloride have been used without any serious toxicity reported, the comment noted that out of this large population of users, some must have been pregnant. The comment contended that this use experience further supports the rat and rabbit fertility and teratogenicity studies. The comment requested that benzethonium chloride be reclassified in Category I for safety.

Although acknowledging that quats are, in general, nonirritating and nontoxic in their effective dosage ranges, the Oral Cavity Panel was concerned about the effect of long-term, daily use of these compounds. The Panel stated that adequate data are not available on: (1) The absorption and attainment of toxic blood levels and the metabolic fate of the quats and (2) the cumulative effects from continued use on a day-to-day basis over the span of years or a lifetime as would be the case when these ingredients are incorporated in mouthwashes (47 FR 22760 at 22860). The Panel was also concerned about the absence of data on the mutagenic, tumorigenic, or teratogenic effects of quats when used on a long-term daily basis in the oral cavity. The Oral Cavity Panel placed most of the quats it evaluated in Category III for safety. Nevertheless, in spite of these concerns, the Panel recommended that benzalkonium chloride and cetalkonium chloride be considered safe for OTC use in the oral cavity.

Regarding the comment's contention that the Oral Cavity Panel was inconsistent in its evaluation of benzethonium chloride and benzalkonium chloride, the agency cannot determine from the Panel's discussion of the two ingredients (47 FR 22760 at 22858 to 22861) what caused the Panel to recommend that one ingredient was safe and the other not safe. However, the Panel made its safety decisions based upon an assumption that oral antiseptics were used on a long-term daily basis. As discussed above, the agency is proposing in this tentative final monograph that data relating to the long-term safety of oral antiseptics is not relevant to the determination of safety for short-term use in the oral cavity (see section I.A., comment 2). Therefore, the agency agrees with the Panel's safety evaluation of benzalkonium chloride and is proposing that benzalkonium chloride is safe for short-term use as an oral antiseptic.

The agency has reevaluated the data submitted to the Oral Cavity Panel as well as new information regarding the safety of benzethonium chloride and concludes that benzethonium chloride should remain in Category III. The agency agrees with the Panel that the studies originally submitted to the Panel (Refs. 1 through 7) do not support the safety of benzethonium chloride.

Regarding the data on absorption and attainment of adequate blood levels and the metabolic fate of quats, the data referred to by the comment (Refs. 1 and 2) do not answer the Panel's concerns. The most meaningful data presented on absorption were contained in the rat maternal and fetal absorption study (Ref. 2). Low levels of C^{14} were detected in maternal blood and urine following oral dosing of pregnant rats with C^{14} labeled benzethonium chloride. After 15 days of dosing with 1.125 milligrams/kilogram (mg/kg) per day labeled benzethonium chloride, 1.5 nanogram/gram of the labeled compound was detected in maternal blood. The urinary level of labeled benzethonium chloride found in this group was 28 nanograms per milliliter (mL). These data suggest poor absorption, but there is no correlation with toxic blood levels. Furthermore, the metabolic fate of benzethonium is unknown and is not addressed in any of the studies mentioned by the comment.

Two studies demonstrate that subcutaneous injection of benzethonium chloride produces fibrosarcomas at the injection site in rats (Ref. 6), but not in mice (Ref. 4). Another study demonstrates that this ingredient is cytotoxic (Ref. 7). These data indicate that benzethonium chloride is a weak carcinogen according to the classification scheme proposed by Grasso and Golberg (Ref. 13).

In one study, rats were injected with the maximally tolerated dose of 3 mg/kg and three lower doses twice weekly for 1 year (Ref. 6). Two hundred animals were treated; 80 were in the high dose group. The study also included 120 each in negative and vehicle control groups. Observation continued for 6 months after termination of treatment. Cumulative data from all dose groups show a 16-percent incidence of tumors at the injection site in males and a 10-percent incidence in females. No injection site tumors were noted in the vehicle control animals; one injection site tumor was observed in the negative control group. At other tested sites, tumor incidence numbers of the treated animals were not different from the control groups. However, there was a clear dose-related effect at the injection site. As stated above, these data indicate that benzethonium chloride is a weak carcinogen.

The teratology studies (Refs. 9, 10, and 12) indicate that benzethonium chloride has very slight teratogenic potential. Effects on the fetus are largely related to the retardation of growth, which is also evident in the dams. Maternal effects also influence fetal viability, especially evident in rabbits (Ref. 12). Increased ossification variations were significant only in the high dose groups (i.e., 35.6 mg/kg/day) in rats (Ref. 10). Effects at lower doses that were apparent in one study (Ref. 9) might be attributed to variability as evidenced by the difference in the two control groups of one of the other studies (Ref. 10). The reproductive capacity of rats does not appear to be affected, although weight gains are affected in both parents (Ref. 8).

The agency does not believe that sufficient data and information are available at this time to categorize benzethonium chloride as safe for use in the oral cavity and invites further comments and data on this matter. The agency is aware that the NTP has undertaken studies to characterize and evaluate the toxicological potential, including carcinogenicity, of benzethonium chloride in laboratory animals. The results of these studies may aid the agency in its determinations regarding the safety of benzethonium chloride. At this time, benzethonium chloride remains in Category III for safety in this tentative final monograph.

References

(1) Research Report No. 23–19, "A Study to Determine Radioactive Residue Levels in Eggs, Tissues, and Excreta from Laying Hens Which Were Fed C^{14}–Hyamine 1622 Sanitized Water," Comment No. C00009, Docket No. 81N–0033, Dockets Management Branch.

(2) "Rat Maternal and Fetal Absorption of C^{14}–Benzethonium Chloride (C^{14}–BTC)," Comment No. C00009, Docket No. 81N–0033, Dockets Management Branch.

(3) Finnegan, J. K. et al., "Pharmacologic Observations on Two Quaternary Ammonium Germicides," Comment No. C00009, Docket No. 81N–0033, Dockets Management Branch.

(4) Kirschstein, R. L., "Toxicology and Carcinogenicity of Preservatives Used in the Preparation of Biological Products," Comment No. C00009, Docket No. 81N–0033, Dockets Management Branch.

(5) "Six Month Toxicity Study with BTC and $ZnCl_2$ on Rats," Comment No. C00009, Docket No. 81N–0033, Dockets Management Branch.

(6) "Toxicology and Carcinogenesis of Various Chemicals Used in the Preparation of Vaccines," Comment No. C00009, Docket No. 81N–0033, Dockets Management Branch.

(7) "Final Report, Contract PH-43-67-677, Project C-173," Comment No. C00009, Docket No. 81N-0033, Dockets Management Branch.

(8) "Project 75-1343, Segment I Rat Fertility Study," Comment No. C00009, Docket No. 81N-0033, Dockets Management Branch.

(9) "Project 75-1344, Segment II Rat Teratology Study," Comment No. C00009, Docket No. 81N-0033, Dockets Management Branch.

(10) "Project 76-1495A, Segment II Rat Teratology Study," Comment No. C00009, Docket No. 81N-0033, Dockets Management Branch.

(11) "Project 75-1345, Segment III Rat Peri and Post Natal Study," Comment No. C00009, Docket No. 81N-0033, Dockets Management Branch.

(12) "Project 75-1346, Segment II Rabbit Teratology Study," Comment No. C00009, Docket No. 81N-0033, Dockets Management Branch.

(13) Grasso, P., and L. Golberg, "Subcutaneous Sarcoma as an Index of Carcinogenic Potency," *Food and Cosmetic Toxicology*, 4:297-320, 1966.

D. Comments on Boric Acid

6. One comment stated that the Oral Cavity Panel's discussion on the safety and effectiveness of boric acid as an antimicrobial ingredient (47 FR 22760 at 22850) should be considered arbitrary because it is based on a limited search of the literature and a minimum effort to evaluate this literature. The comment contended that the Panel's statements that "absorption of boric acid occurs readily from the mucous membranes of the mouth, throat * * * " and that "it is also absorbed from the surface of the vagina, the lining of the conjunctival sac * * *" (47 FR 22850) are not mentioned in the discussion of this ingredient in the paper by George (Ref. 1) which the Panel cited as the source of this information. The comment added that the only statement this author makes regarding mucous membrane absorption of boric acid is an inference taken from another reference (Ref. 2), which in turn provided no chemical or laboratory evidence to support the previous statements.

The comment also objected to the Oral Cavity Panel's statement "Death has occurred from ingestion of less than 5 grams (g) [of boric acid] in infants and from 5 to 20 g in adults," (47 FR 22760 at 22850), stating that these reported lethal doses are found in review articles and appear repeatedly as a result of frequent cross-referencing from publications used in the medical field. The comment contended that the only absolute statement on a toxic dose of boric acid appeared in a 1906 New York Medical Bulletin which discussed an autopsy report on a 62-year-old man who had ingested 15 g of boric acid on prescription for a bladder infection; however, no conclusion was made that boric acid was the cause of death. The comment added that the published reports on poisonings by boric acid resulted from special circumstances, i.e., in the course of therapeutic treatments, erroneous use of boric acid in place of other substances in hospitals, or similar misuse, and usually only estimated dosages were reported. Although the comment stated that boric acid should not be used indiscriminately, it contended that the Panel made an inadequate study of the literature concerning the safety of boric acid. The comment added that the only carefully controlled clinical study on the ingestion of borax and boric acid by humans was a study by Wiley, published in 1904 (Ref. 3). The comment expressed surprise that this reference was not cited by the Panel and has not been cited by other authors who have conducted a literature review on boric acid. The comment reported that this study, conducted by the "poison squad" who eventually made up the staff of FDA, involved ingestion of borax or boric acid at varying dosages up to 5 g per day (as a single dose) for periods up to 50 days. The comment claimed that no fatalities or chronic irreversible pathological conditions were observed in any of the participants.

The comment also expressed concern about the Oral Cavity Panel's classification of boric acid in Category II for effectiveness (47 FR 22760 at 22850) on what it considered a minimum effort to investigate and evaluate the literature. For example, the comment mentioned that the Panel cited a paper by Novak and Taylor (Ref. 4). In this study, the investigators found that concentrations higher than 2 percent boric acid may inhibit phagocytosis. The comment contended that although the Panel acknowledged this finding, it ignored the absence of this action at lower concentrations. The comment also referred to another paper by these same authors (Ref. 5), which discusses the antibacterial action of boric acid. The comment stated that this article appeared in the same journal immediately following the article by Novak and Taylor but was not cited by the Panel in its list of references on boric acid. The comment concluded that the references cited as evidence to support the Panel's conclusions on effectiveness are limited to one reference, which is general in nature with no primary references or data presented.

The agency has reviewed the article by George (Ref. 1) cited in the Oral Cavity Panel's report and the reference cited therein (Ref. 2) and agrees with the comment that these references do not present adequate evidence to support the Panel's conclusion that boric acid is absorbed from mucous membranes. Although the literature contains many incidences of boric acid toxicity resulting from the absorption of the drug after application to abraded skin or from ingestion, there is a lack of data and information on the degree of absorption of boric acid from mucous membranes (Refs. 6 through 9).

The agency agrees with the comment that the human lethal doses used in the Oral Cavity Panel's report appear in review articles and other biomedical publications as a result of cross-referencing from older literature. However, because most reports of poisoning with boric acid are due to accidental ingestion of the drug, exact doses cannot be determined; thus, varying human lethal doses, such as 15 to 30 g in adults and 3 to 6 g in children, are reported in the literature (Refs. 8, 9, and 10).

The agency notes that the study by Wiley (Ref. 3) was conducted to determine the effects of borax and boric acid upon digestion and overall human health. At the end of this study, Wiley reported that the continuous administration of borax and boric acid created disturbances of appetite, digestion, and health.

As more reports of the toxic effects of boric acid appeared and more effective antiseptics were developed, the Vaginal Panel noted that this ingredient fell into disfavor except for a few minor uses (48 FR 46694 at 46712). This may have been due in part to the findings of Novak and Taylor (Ref. 4) who suggested that normal phagocytosis is inhibited by boric acid in concentrations greater than 2 percent, thus counteracting the drug's antibacterial action.

The agency reviewed the second study by Novak and Taylor (Ref. 5) and notes that this in vitro study was designed to determine the bacteriostatic action of boric acid, in the presence of tears, against three species of bacteria commonly found in minor eye infections. The authors reported that boric acid in concentrations from 0.5 to 2 percent was bacteriostatic against the three species of bacteria tested. However, the agency does not consider this in vitro study to be a valid substitute for a well-controlled clinical study in the intended target population. The agency believes that the Panel did not include this study in the list of references cited for boric acid because it did not consider the study relevant to the efficacy of this ingredient in OTC oral health care drug products. The

agency concludes that this study does not support the effectiveness of boric acid for antiseptic use in OTC oral health care drug products.

The agency points out that the Oral Cavity Panel's discussion concerning the safety and effectiveness of boric acid was not intended to include all available information on the subject, but was intended to be representative of the available data. The Panel members selected the studies to be cited according to their best scientific judgment at that time. In addition, because the comment did not submit new data or information that offer evidence contrary to the Panel's conclusion and other information that exists in the literature (as discussed above), the agency is proposing in this tentative final monograph that boric acid remain in Category II (not safe and not effective) as an antiseptic agent in OTC oral health care drug products.

References

(1) George, A. J., "Toxicity of Boric Acid through Skin and Mucous Membranes," *Food and Cosmetic Toxicology*, 3:99–101, 1965.

(2) Gleason, M. N. et al., "Borate Section III, Therapeutics Index" in "Clinical Toxicology of Commercial Products: Acute Poisoning (Home & Farm)," The Williams and Wilkins Co., Baltimore, p. 122, 1957.

(3) Wiley, H. W., "1. Boric Acid and Borax," in "Influence of Food Preservatives and Artificial Colors on Digestion and Health," U. S. Department of Agriculture, Bureau of Chemistry-Bulletin No. 84, pp. 254–255, 1904.

(4) Novak, M., and W. I. Taylor, "Phagocyticidal and Antibacterial Action of Boric Acid," *Journal of the American Pharmaceutical Association* (Scientific Edition), 40:428–430, 1951.

(5) Novak, M., and W. I. Taylor, "Antibacterial Action of Boric Acid in Lacrima (Tears)," *Journal of the American Pharmaceutical Association* (Scientific Edition), 40:430–432, 1951.

(6) Pfeiffer, C. C. et al., "Boric Acid Ointment: A Study of Possible Intoxication in the Treatment of Burns," *Journal of the American Medical Association*, 128:266–274, 1945.

(7) Goldbloom, R. B., and A. Goldbloom, "Boric Acid Poisoning—Report of Four Cases and a Review of 109 Cases from the World Literature," *The Journal of Pediatrics*, 43:631–643, 1953.

(8) Kingma, H., "The Pharmacology and Toxicology of Boron Compounds," *Canadian Medical Association Journal*, 78:620–622, 1958.

(9) McNally, W. D., and C. A. Rust, "The Distribution of Boric Acid in Human Organs in Six Deaths Due to Boric Acid Poisoning," *Journal of the American Medical Association*, 90:382–383, 1928.

(10) Valdes-Dapena, M. A., and J. B. Arey, "Boric Acid Poisoning: Three Fatal Cases with Pancreatic Inclusions and a Review of the Literature," *Journal of Pediatrics*, 61:531–546, 1962.

7. Referring to the Oral Cavity Panel's statement that "Boric acid is used as a pharmaceutical necessity for buffering as well as for an active ingredient (Ref. 1)" (47 FR 22760 at 22850), one comment stated that the cited reference discusses only the use of boric acid as a pharmaceutical necessity, but not as a buffer or as an active ingredient. The comment contended that the Panel's statement as written gives the connotation that the buffering action of boric acid and its use as an active ingredient are both cited in the reference. The comment recommended that the statement be amended to read "Boric acid is used as a pharmaceutical necessity (Ref. 1) for buffering * * *."

The comment is correct in stating that the cited pages of the National Formulary (Ref. 1) discuss the use of boric acid as a pharmaceutical necessity, but the cited pages do not discuss its use as a buffer or as an active ingredient. The agency notes, however, that boric acid is discussed as a buffering agent on pages 935 to 936 of the same reference (Ref. 2), and that these pages should have been included as part of the citation. The agency also agrees with the comment that the National Formulary does not discuss the use of boric acid as an active ingredient.

References

(1) "National Formulary," 14th ed., American Pharmaceutical Association, Washington, pp. 776–777, 1975.

(2) "National Formulary," 14th ed., American Pharmaceutical Association, Washington, pp. 935–936, 1975.

E. Comments on Cetylpyridinium Chloride

8. Two comments contended that cetylpyridinium chloride at concentrations of up to 0.1 percent is safe for use as an OTC antiseptic agent and should be placed in Category I. The first comment described the results of various safety testing (e.g., acute toxicity, oral mucosal and eye irritation, subchronic, and teratology studies) on cetylpyridinium chloride alone and on cetylpyridinium chloride in combination with domiphen bromide. The comment also submitted a safety report (Ref. 1) prepared from data available through August, 1982. The comment stated that, in all these studies, there have been no remarkable pathologic findings and thus 0.045 percent cetylpyridinium chloride is safe for OTC oral use as a single ingredient and in combination with 0.005 percent domiphen bromide.

The other comment stated that cetylpyridinium chloride is the active ingredient in a commercially available mouthwash that has been used by millions of consumers for over 40 years and that the product continues to be the subject of an approved application based on the established safety of the product. The comment summarized the safety data that had been submitted to the Oral Cavity Panel, including long-term usage studies involving acute and subacute toxicity exposure to cetylpyridinium chloride and related compounds in humans and animals (Ref. 2). The comment contended that these studies failed to reveal evidence of any teratogenic effects and added that in studies involving life time exposure of mice and rats to benzalkonium chloride, a representative quat, no evidence of carcinogenic or mutagenic potential was found. The comment concluded that these experimental data, in conjunction with the extremely low order of toxicity seen in the more than four decades of human use, reinforce and justify the National Cancer Institute's (NCI) apparent lack of concern regarding the carcinogenicity and mutagenicity of cetylpyridinium chloride and other quats.

The comment added that the safety of cetylpyridinium chloride is further substantiated by the infrequent number of adverse drug experience reports, particularly when considered in relation to the extensive usage of products containing this ingredient. For example, marketing studies in 1979 indicated that one mouthwash product was used by approximately 13 million consumers and that 500,000 people had used the product more or less continuously for a 10-year period. The comment stated that, in the 20-year period between 1963 and 1982, there were only 110 drug experience reports, an average of 5.5 reports per year. The comment contended that these reports show that cetylpyridinium chloride is safe because it has not been associated with any deleterious effects of a significant nature when routinely used as an oral hygiene product. The comment also submitted the results of several clinical evaluations of irritation and/or allergic reactions of mucous membrane and skin surface exposure to cetylpyridinium chloride-containing solutions (Ref. 3). The comment concluded that the drug experience reports and clinical evaluations support a Category I classification of cetylpyridinium chloride for safety.

As part of FDA's Drug Efficacy Study Implementation (DESI) program, mouthwash products containing povidone-iodine, cetylpyridinium chloride, and other ingredients were reviewed by the National Academy of Sciences-National Research Council,

Drug Efficacy Study Group (NAS-NRC/DESG) and found ineffective for claims relating to antimicrobial, antiseptic, germicidal, and analgesic uses (35 FR 12423). In a subsequent notice published in the **Federal Register** of December 2, 1971 (36 FR 23000), the agency stated that because of the implementation of the OTC drug review, mouthwash and gargle products reviewed under the DESI program would now be under the purview of the OTC drug review; thus, final agency action on these products would be deferred pending evaluation of the data and information concerning such products under the OTC drug review.

The agency believes that many of the oral antiseptic ingredients reviewed by the Oral Cavity Panel, including cetylpyridinium chloride, were placed in Category III for safety because they were used commercially in mouthwashes that were recommended for long-term use on a daily basis. The agency believes that the Panel's concerns regarding the safety of the long-term OTC use of oral antiseptic ingredients are not necessarily relevant to the short-term OTC use of these ingredients (see section I.A., comment 2).

The Oral Cavity Panel discussed the results of several cetylpyridinium chloride toxicity studies in its report (47 FR 22760 at 22865). According to the Panel, the LD_{50} of cetylpyridinium chloride is 250 kg/mg subcutaneously, 6 mg/kg intraperitoneally, 30 mg/kg intravenously, and 200 mg/kg orally. When 50 mg/kg cetylpyridinium chloride in water was administered daily for 60 days to rats, no toxic effects or alterations in the rate of growth were noted. Doses of 5 to 10 mg/kg administered through the esophagus showed no toxic effects over a 6-day period.

The Panel noted that a 1:3,000 (0.033 percent) solution of cetylpyridinium chloride is irritating to the mucous membranes of the conjunctiva, but not to the skin (47 FR 22865). It also stated that a 1:200 (0.5 percent) alcoholic or aqueous solution of cetylpyridinium chloride does not cause skin irritation. The Panel added that percutaneous absorption of cetylpyridinium chloride is not believed to be significant. However, the agency notes that the presence of the cetyl group on the basic quat molecule increases the lipid solubility of the molecule and, thus, cetylpyridinium chloride has a potential for increased absorption and irritation (47 FR 22865).

The agency has reviewed its adverse reaction files covering 1969 to August 1993 (Ref. 4). During those years, 249 cases of adverse reactions were associated with the use of products containing cetylpyridinium chloride. None of the adverse reaction reports could be attributed solely to cetylpyridinium chloride. Of these cases, 10 had a serious outcome (e.g., death, coma, or hospitalization). Two reports involved children under 4 years of age who died after ingesting unknown amounts of a mouthwash containing cetylpyridinium chloride and 14 percent alcohol. In both cases, alcohol was the most likely cause of death.

Four adverse reaction reports described coma as an outcome. Two involved young children (3 and 4 years old) who lapsed into comas after ingesting unknown amounts of a mouthwash product containing cetylpyridinium chloride and 14 percent alcohol. As is the case with the deaths described above, these comas are more likely due to alcohol ingestion than cetylpyridinium chloride ingestion. One adverse reaction report in which coma is listed as the outcome involved an individual who ingested 44 cetylpyridinium chloride-containing lozenges, became gradually and imperceptively unconscious, and caused a head-on automobile collision. Another report described a middle-aged male with a history of alcoholism who was hospitalized in a coma after possibly ingesting a mouthwash containing cetylpyridinium chloride.

Two anaphylactic-type reactions were reported. One was determined to be an allergic reaction to bisulfites. The other was not clear-cut because the subject had experienced several similar anaphylactic-like attacks, only one of which followed use of a cetylpyridinium chloride-containing product.

Two cases reported the hospitalization of people who had severe allergic-type reactions. One report described a 21-year-old female with swelling in her throat, a sensation of feeling hot and flushed, followed by dyspnea, dysphagia, angioedema of the face (especially the eyelids), hands, and feet, and near faintness following the ingestion of one cetylpyridinium chloride lozenge. Another case report described a young male (8 years old) with a burning sensation, redness, and swelling on areas of the skin (chin and neck) where a cetylpyridinium chloride-containing mouthwash was spilled during gargling.

The most frequently reported less serious events are as follows: 26 cases of stomatitis, 13 reports of pain, 12 reports of taste perversion, 10 cases of nausea, 9 cases of contact dermatitis, 9 cases of pharyngitis, 8 cases of malaise, and 7 cases of allergic responses. Other less frequently reported reactions included rash, tooth caries, dry mouth, and rhinitis.

The agency believes that the information contained in its adverse reaction files regarding cetylpyridinium chloride demonstrates that the ingredient can be safely used in an OTC drug product. None of the adverse reaction reports could be attributed solely to cetylpyridinium chloride. All reports involved products containing many ingredients in addition to cetylpyridinium chloride. In addition, other drugs (e.g., alcohol) were implicated in the most serious cases.

The agency believes that the information contained in its adverse reaction files, 30 years of safe marketing of an OTC mouthwash containing cetylpyridinium chloride (NDA 14-598), and the safety data evaluated by the Oral Cavity Panel are sufficient to conclude that 0.025 to 0.1 percent cetylpyridinium chloride is safe as an OTC oral antiseptic when labeled for short-term use (not to exceed 7 days). However, the agency is concerned that using cetylpyridinium chloride where excessive gum irritation or bleeding exists could increase the absorption and systemic load of the ingredient and possibly lead to some of the toxicological effects discussed by the Oral Cavity Panel (e.g., neuromuscular blocking of nicotinic and muscarinic receptors) (47 FR 22760 at 22865). Therefore, the agency is proposing labeling that would caution consumers not to use a product containing cetylpyridinium chloride if excessive gum irritation or bleeding exists unless directed to do so by a doctor or dentist as follows: "Do not use this product if gums are irritated or bleeding unless directed to do so by a doctor or dentist." This labeling will be included in the final monograph for OTC oral antiseptics if cetylpyridinium chloride becomes Category I in that rulemaking. The agency requests comment regarding this proposed labeling.

Data on the combination of cetylpyridinium chloride and domiphen bromide are discussed in section I.L., comments 30 and 31.

References

(1) Comment No. C00013, Docket No. 81N-0033, Dockets Management Branch.

(2) OTC Vol. 130167.

(3) Attachment C, Comment No. C00015, Docket No. 81N-0033, Dockets Management Branch.

(4) Food and Drug Administration, Center for Drug Evaluation and Research, Adverse Reaction Summary Listing for Cetylpyridinium Chloride for the years 1969

to August 1993, OTC Vol. 13CTFM, Docket No. 81N–0033, Dockets Management Branch.

9. Two comments contended that 0.025 to 0.1 percent cetylpyridinium chloride is an effective antiseptic agent and should be placed in Category I. One comment stated that complete proof of the ability of cetylpyridinium chloride to kill bacteria in vitro had been submitted to the Oral Cavity Panel (Ref. 1) and that this proof had been accepted at the time by the Panel. The comment also discussed several tests (Ref. 2) purporting to demonstrate the effectiveness of 0.045 percent cetylpyridinium chloride in combination with 0.005 percent domiphen bromide and stated that these tests supported the antiseptic effectiveness of cetylpyridinium chloride. The other comment discussed data from seven in vitro studies designed to demonstrate the antiseptic activity of cetylpyridinium chloride (Ref. 3). The comment stated that two of these studies fulfilled the in vitro guidelines established by the Oral Cavity Panel (47 FR 22760 at 22890 to 22893) and that the other five studies demonstrated complementary activity against other test organisms (Ref. 3). The comment also summarized a number of in vivo studies designed to demonstrate the antimicrobial activity of cetylpyridinium chloride. The comment mentioned that all of these in vitro and in vivo studies had been submitted to the Oral Cavity Panel.

That Panel discussed in vitro and in vivo testing protocol guidelines for upgrading oral antiseptic ingredients to Category I (47 FR 22760 at 22890 to 22893). The in vitro studies submitted by the second comment (Ref. 3) do not fulfill the guidelines recommended by the Panel. For example, in one study (Ref. 4), the protocol closely resembled that recommended by the Panel. However, the incubation conditions used to prepare the test cultures were unlike those recommended by the Panel, and some culture conditions were not specified (i.e., whether the cultures were grown aerobically or anaerobically). The test method used in this study was also different from the method recommended by the Panel in that culture tubes that showed no growth after 48 hours incubation were not transferred to 90 mL of sterile inactivating media and further incubated for 1 week. In another study where the protocol was similar to that recommended by the Panel (Ref. 5), a product containing cetylpyridinium chloride was used as the test material, but cetylpyridinium chloride alone was not tested. Therefore, there is no way of knowing whether or not other ingredients in the test product affected its antimicrobial activity. Several other in vitro studies (Refs. 6 through 9) tested the antiseptic effectiveness of cetylpyridinium chloride and cetylpyridinium chloride-containing products against organisms other than those recommended by the Panel. One study (Ref. 10) tested the effectiveness of several mouthwash formulations against pooled human saliva. Critical killing times against the organisms in the saliva were determined, but specific organisms were not identified.

Fifteen of the in vivo studies submitted were based upon plaque reduction. The Panel had considered using plaque reduction as a criterion for antiseptic activity in the oral cavity, but discarded it (47 FR 22760 at 22840). The Panel did not accept plaque reduction as a criterion for determining the effectiveness of oral antiseptics, and the agency agrees. A subsequent segment of the rulemaking for OTC oral health care drug products will cover plaque-related claims and ingredients used for the reduction of plaque. (See section I.A., comment 1 and section I.M., comment 32.)

The agency believes that the other in vivo studies submitted (Ref. 3) are not adequate to demonstrate the effectiveness of cetylpyridinium chloride in reducing the bacterial population of the oral cavity. These studies were not designed to demonstrate the antibacterial activity of the ingredient cetylpyridinium chloride alone. They were designed to demonstrate the antibacterial activity of products such as commercial mouthwashes or lozenges containing cetylpyridinium chloride and other ingredients that could affect the antibacterial activity of the product. The complete formulations of these products were not identified, and the antiseptic activity of the ingredient cetylpyridinium chloride was not compared to the activity of a placebo containing all of the ingredients in the commercial product except for the cetylpyridinium chloride. Therefore, any antiseptic activity demonstrated in those studies cannot be solely attributed to the presence of cetylpyridinium chloride. In order to demonstrate antiseptic activity of cetylpyridinium chloride, studies must be designed with one arm consisting of the ingredient cetylpyridinium chloride alone to demonstrate that cetylpyridinium chloride decreases the number of microorganisms in the oral cavity. In addition, the agency is not aware of any data from clinical studies demonstrating a therapeutic benefit from the OTC use of cetylpyridinium chloride as an antiseptic in the oral cavity. Data on the combination of cetylpyridinium chloride and domiphen bromide are discussed in section I.L., comments 30 and 31.

The agency concludes that additional data are needed to establish the effectiveness of cetylpyridinium chloride as an oral antiseptic to help prevent infection in the oral cavity. The agency believes that the Panel's proposed in vitro and in vivo testing guidelines and its discussion of clinical studies represent a good starting point for the design of studies to upgrade a Category II or Category III oral antiseptic ingredient to Category I. (See section I.M., comment 33 for a further discussion of testing guidelines.) However, the agency notes that specific testing guidelines for upgrading ingredients to monograph status are not included in the tentative final monograph. (See part II. paragraph A.2.—*Testing of Category II and Category III conditions.*) All such testing should be designed using the most current technology available. The agency will meet with industry representatives or other interested parties at their request to discuss testing protocols. Any party interested in conducting studies should request a meeting at its earliest convenience.

References

(1) OTC Vols. 130007 through 130011, 130089, 130090, and 130167 through 130171.

(2) Comment No. C00013, Docket No. 81N–0033, Dockets Management Branch.

(3) Comment No. C00015, Docket No. 81N–0033, Dockets Management Branch.

(4) Project Report No. M–75–03, OTC Vol. 130167.

(5) Project Report No. M–77–03, OTC Vol. 130167.

(6) Project Report No. M–76–05, OTC Vol. 130167.

(7) Myers, G. E., J. K. Logan, and V. J. Mitchell, "Microbiological Problems in Oral Hygiene," OTC Vol. 130167.

(8) "An In-Vitro Evaluation of Cepacol," OTC Vol. 130167.

(9) Hicks, G. F., L. L. Nisonger, and I. Ruchman, "Germicidal Effects of Various Combinations of Cetyl Pyridinium Chloride Against Antibiotic-Resistant *Staphylococci*," OTC Vol. 130167.

(10) "Comparison of the Antibacterial Activity of Colgate 100®, Listerine®, Lavoris®, Micrin®, and Cepacol®," OTC Vol. 130167.

F. Comments on Chlorophyllin Copper Complex

10. One comment complained that the Oral Cavity Panel's discussion of chlorophyllin under the heading "Antimicrobial Agents" (47 FR 22760 at 22866 to 22867) contains inaccurate and misleading statements about other

properties of the ingredient. The comment specifically objected to the statement that chlorophyllin "has fallen into disuse over recent years since it has not been demonstrated that it is an effective deodorant" and added that support for this statement was one unidentified reference to a study in which ingested chlorophyll decreased halitosis in dogs but had no effect on the odor in the dogs' coats (hair).

The comment maintained that 15 laboratory and human clinical studies demonstrating the deodorancy effectiveness of chlorophyll were submitted to the Panel (Ref. 1). Emphasizing that chlorophyllin has not fallen into disuse as a deodorant, the comment asserted that chlorophyllin is widely used in hospitals and nursing homes as a deodorant for ostomy patients and incontinent patients. The comment cited an article by Young and Beregi (Ref. 2) to support the wide use of chlorophyllin as an aid in controlling odors of incontinent patients. The comment suggested that "a less frequent but pertinent" indication for chlorophyllin is to reduce odor from cancer of the oral cavity.

The agency notes that chlorophyllin copper complex is the name adopted for chlorophyllin by the United States Adopted Names Council (Ref. 3). Therefore, chlorophyllin copper complex is the name used for this ingredient in this tentative final monograph.

The agency agrees with the comment that chlorophyllin copper complex is appropriate for use in hospitals and nursing homes as an internal deodorant for ostomy patients and incontinent patients. In the final monograph for OTC deodorant drug products for internal use published in the **Federal Register** of May 11, 1990 (55 FR 19862), the agency concluded that chlorophyllin copper complex (100 to 200 mg daily) is generally recognized as safe and effective for OTC (internal) use in controlling ostomy odors and in controlling the odors of fecal and urinary incontinence. The agency considers the local deodorancy effect of chlorophyllin copper complex when used topically in the oral cavity to be a cosmetic rather than a drug effect and, as such, would not be subject to the rulemaking for OTC oral health care drug products. (For a discussion of the cosmetic uses of OTC oral health care drug products, see section I.A., comment 3.) However, if a product containing this ingredient makes a claim that the product "reduces odor from cancer of the oral cavity," this claim would need to be supported by data from appropriate studies in patients with cancer of the oral cavity.

References

(1) OTC Vol. 130015.

(2) Young, R. W., and J. S. Beregi, Jr., "Use of Chlorophyllin in the Care of Geriatric Patients," *Journal of the American Geriatrics Society*, 28:46, 1980.

(3) "USAN and the USP Dictionary of Drug Names," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 136, 1993.

11. Noting that the Oral Cavity Panel had classified chlorophyllin solely as an "antimicrobial agent," one comment stated that its antibacterial properties are less significant than its healing effects. The comment asserted that the data submitted to the Panel emphasized that chlorophyllin is primarily a healing agent that acts to relieve discomfort due to minor irritations, inflammation, and other lesions by encouraging tissue repair and reducing inflammation. The comment contended that there should be a classification for ingredients, such as chlorophyllin, that encourage repair of minor irritations or inflammation. Acknowledging that there might be some problems with using the term "healing agents" for OTC drug products, the comment suggested using the term "tissue-repair agents" for products containing this ingredient. The comment referred to the statement in the Panel's report that no data were submitted or are available from controlled studies to substantiate a wound healing claim (47 FR 22760 at 22867) and argued that its own submission to the Panel contained many controlled studies on the wound healing effects of chlorophyllin.

The agency has reviewed the submissions on chlorophyllin copper complex made to the Oral Cavity Panel (Refs. 1 and 2) as well as submissions made to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (Dental Panel) (Refs. 3 and 4). Although no antiseptic claims appear in the labeling of chlorophyllin copper complex-containing products submitted to these panels, the submissions contain data purporting to show the bacteriostatic effectiveness of water-soluble chlorophyllins as well as data to support the wound healing claims (Refs. 1 and 3). The Oral Cavity Panel evaluated the data submitted in support of the antiseptic effectiveness of chlorophyllin copper complex, and the Dental Panel evaluated the data submitted to support the wound healing claims.

The Oral Cavity Panel concluded that chlorophyllin copper complex is safe, but that there are insufficient data available to permit final classification of its effectiveness as an OTC antiseptic active ingredient for topical use on the mucous membranes of the mouth and throat (47 FR 22760 at 22866). Because no additional data were submitted to the agency in support of the antiseptic effectiveness of chlorophyllin copper complex, the agency concludes that the Panel's Category III classification is appropriate. Therefore, in this tentative final monograph, the agency is proposing a Category III classification for chlorophyllin copper complex as an OTC oral health care antiseptic ingredient.

In its report on OTC oral mucosal injury drug products published in the **Federal Register** of November 2, 1979 (44 FR 63270), the Dental Panel concluded that water-soluble chlorophyllins are safe, but that there were insufficient effectiveness data available to permit final classification of water-soluble chlorophyllins as oral wound healing agents (44 FR 63270 at 63286). Therefore, the Dental Panel classified water-soluble chlorophyllins in Category III. In response to the publication of the Panel's report, the agency received no comments regarding chlorophyllin copper complex as an OTC oral wound healing agent. Therefore, in the tentative final monograph for OTC oral mucosal injury drug products published in the **Federal Register** of July 26, 1983 (48 FR 33984), the agency accepted the Panel's evaluation and proposed a Category III classification for chlorophyllin copper complex as an oral wound healing agent. Again, the agency received no comments regarding chlorophyllin copper complex in response to the publication of the tentative final monograph for OTC oral mucosal injury drug products. Accordingly, in the final rule for OTC oral wound healing agents published in the **Federal Register** of July 18, 1986 (51 FR 26112), the agency concluded that there was insufficient evidence to support the effectiveness of chlorophyllin copper complex as an oral wound healing agent. Therefore, chlorophyllin copper complex is considered a nonmonograph oral wound healing ingredient.

References

(1) OTC Vol. 130015.
(2) OTC Vol. 130088.
(3) OTC Vol. 080043.
(4) OTC Vol. 080168.

G. Comments on Domiphen Bromide

12. One comment requested that the agency approve domiphen bromide at concentrations of up to 0.1 percent for safety. The comment described the results of various safety testing (e.g.,

acute toxicity, oral mucosal and eye irritation, subchronic, and teratology studies) on domiphen bromide alone and on domiphen bromide in combination with cetylpyridinium chloride. The comment also included a safety report (Ref. 1) prepared from data available through August 1982. The comment stated that, in all these studies, there have been no remarkable pathologic findings and thus up to 0.1 percent domiphen bromide is safe for OTC oral use as a single ingredient.

As stated in section I.A., comment 2, the agency believes that many of the oral antiseptic ingredients reviewed by the Oral Cavity Panel, including domiphen bromide, were placed in Category III for safety because they were used commercially in mouthwashes that were recommended for long-term use on a daily basis. The agency believes that the Panel's concerns regarding the safety of the long-term OTC use of oral antiseptic ingredients are not necessarily relevant to the short-term OTC use of these ingredients.

The agency has reevaluated the data submitted to the Oral Cavity Panel regarding the safety of domiphen bromide in light of labeling that would limit use of oral antiseptic drug products to 7 days or less. The Panel noted in its discussion of domiphen bromide (47 FR 22760 at 22868 to 22869) that "the concentrations of domiphen bromide used in commercial lozenges and mouthwashes appear to be nontoxic." It cited several studies in which no toxicity could be demonstrated. According to the Panel, the intravenous LD_{50} was determined to be 18 mg/kg for rats, 31 mg/kg for mice, and 11 to 12 mg/kg for rabbits. An oral LD_{50} (species unspecified) could not be determined because marked diarrhea resulted, but it was suspected to be above 800 mg/kg/day. The intraperitoneal LD_{50} was 40 to 45 mg/kg for rats and 10 to 20 mg/kg for guinea pigs. One study (Ref. 2) discussed in the Panel's report concluded that clinical use of a mouthwash containing 0.01 percent domiphen bromide two to six times daily for up to 52 weeks resulted in no apparent toxicity.

The Panel noted that only six adverse reactions were reported between 1958 and 1970 for a lozenge product containing domiphen bromide (47 FR 22869). These included one complaint of lack of effectiveness, two cases of burns on the tongue, one case of soreness of the mouth, one case of fungal growth after use of the product, and one case of chalk-like taste. The agency has reviewed its adverse reaction files covering 1969 to May 1993. During those years, no adverse event reports associated with domiphen bromide were received.

The agency tentatively concludes that the safety data evaluated by the Oral Cavity Panel, 30 years of safe marketing of an OTC mouthwash product containing domiphen bromide (NDA 14–598), and the lack of adverse event reports in its files are sufficient to conclude that up to 0.1 percent domiphen bromide is safe as an OTC oral antiseptic when labeled for short-term use (not to exceed 7 days). However, when this ingredient is used in conjunction with cetylpyridinium chloride as an oral antiseptic (see section I.E., comment 8), the agency is concerned that using domiphen bromide where excessive gum irritation or bleeding exists could increase the absorption and systemic load of the ingredient and possibly lead to some of the toxicological effects discussed by the Oral Cavity Panel (e.g., convulsions, central nervous system depression followed by death due to the curare-like action of quats) (47 FR 22760 at 22869). Therefore, the agency is proposing labeling that would caution consumers not to use a product containing domiphen bromide if excessive gum irritation or bleeding exists unless directed to do so by a doctor or dentist as follows: "Do not use this product if gums are irritated or bleeding unless directed to do so by a doctor or dentist." This labeling will be included in the final monograph for OTC oral antiseptics if domiphen bromide becomes Category I in that rulemaking. The agency requests comment regarding this proposed labeling.

Data on the combination of cetylpyridinium chloride and domiphen bromide are discussed in section I.L., comments 30 and 31.

References

(1) Comment No. C00013, Docket No. 81N–0033, Dockets Management Branch.

(2) Kutscher, A. H., and J. Budowsky, "Observations on the Clinical Use of Bradosol," *Oral Surgery, Oral Medicine, and Oral Pathology*, 7:873–875, 1954.

13. One comment requested that the agency approve 0.05 percent domiphen bromide for effectiveness. The comment stated that effectiveness was proven in tests against three organisms, and that the results of these tests were included in the comment (Ref. 1) and had been reported to the Oral Cavity Panel (Ref. 2). The comment added that the protocol for these studies was reviewed and approved by the Panel. The comment mentioned that, in several votes taken over a period of more than 3 years, the Panel placed domiphen bromide in Category I. The comment added that, at its next-to-last meeting, the Panel rescinded its action and placed domiphen bromide, along with all other antiseptic ingredients, in Category III for effectiveness. The comment argued that the Panel's decision was ill-advised and urged the agency to give monograph status to domiphen bromide.

The agency believes that there are not enough data to conclude that domiphen bromide is an effective oral antiseptic. The effectiveness studies (Refs. 1 and 2) were conducted according to the July 12, 1977, version of tentative guidelines developed and submitted to the Panel by the NDMA (formerly known as The Proprietary Association) (Ref. 3). Those guidelines were under consideration by the Oral Cavity Panel, but were subsequently revised as described in the Panel's 1982 report (47 FR 22760 at 22890 to 22893). A notable revision made by the Panel was to increase the inoculum of test culture; the 1977 NDMA guidelines provided for a 1 mL aliquot of a 1 to 4 dilution of inoculum added to 10 mL of the mouthwash product or active ingredient, while the Panel's final guidelines specified 1 mL of undiluted culture in 9 mL of product or active ingredient. The Panel also proposed additional in vitro testing that included a determination of the minimum inhibitory concentration (MIC) of the antiseptic agent, and testing of freshly obtained clinical isolates from mouth and throat infections to provide updated, relevant data on the susceptibility of these isolates to the antiseptic agent (47 FR 22760 at 22890 to 22891). Since publication of the Panel's report, no such data for domiphen bromide have been provided to the agency. In addition, the agency is not aware of any data from clinical studies demonstrating a therapeutic benefit from the OTC use of domiphen bromide in the oral cavity. The agency concludes that additional data are necessary to establish the effectiveness of domiphen bromide as an oral antiseptic to help prevent infection in the oral cavity.

The agency believes that the Panel's 1982 proposed testing guidelines and its discussion of clinical studies represent a good starting point for the design of studies to upgrade a Category II or Category III oral antiseptic ingredient to Category I. (See section I.M., comment 33 for a further discussion of testing guidelines.) Since testing requirements are subject to change over time because of technological advancements, the agency notes that specific testing guidelines for upgrading ingredients to monograph status are not included in the tentative final monograph. (See part

II. paragraph A.2.—*Testing of Category II and Category III conditions.*) All such testing should be designed using the most current technology available. The agency will meet with industry representatives or other interested parties at their request to discuss testing protocols. Any party interested in conducting studies should request a meeting at its earliest convenience.

References

(1) Comment No. C00013, Docket No. 81N–0033, Dockets Management Branch.
(2) OTC Vol. 130134.
(3) OTC Vol. 130131.

H. Comment on Phenol

14. One comment requested that the agency classify 1.4 to 1.5 percent phenol in Category I as an antiseptic mouthwash. The comment stated that until its next-to-last meeting, the Oral Cavity Panel believed that the antiseptic capability of a mouthwash could be demonstrated through the use of in vitro and in vivo studies, but that the Panel arbitrarily decided to reverse its long-standing position without additional evidence. The comment further stated it had presented documentation to the Panel prior to its reversal that phenol met the requirements of both the in vitro and in vivo protocols. The comment resubmitted the same studies it had submitted to the Panel and requested that the agency accept these data (Ref. 1).

The agency has evaluated the studies submitted to the Panel and concludes that they are not adequate to establish the effectiveness of phenol as an OTC oral antiseptic. The comment's data include one in vitro study and two in vivo efficacy studies. No data from clinical studies were submitted to the agency to demonstrate a therapeutic benefit from the OTC use of phenol in the oral cavity.

The in vitro study was conducted according to the July 12, 1977, NDMA tentative guidelines that had been submitted to the Panel (Ref. 2). Those guidelines were under consideration by the Oral Cavity Panel at the time the comment's studies were conducted, but were subsequently revised as described in the Panel's report (47 FR 22760 at 22890). A notable revision made by the Panel was to increase the inoculum of test culture; the 1977 NDMA guidelines provided for a 1 mL aliquot of a 1 to 4 dilution of inoculum added to 10 mL of the product or active ingredient, while the Panel's final guidelines specified 1 mL of undiluted culture in 9 mL of product or active ingredient. The Panel also proposed additional in vitro testing that included a determination of the MIC of the antiseptic agent, and testing of freshly obtained clinical isolates from mouth and throat infections to provide updated, relevant data on the susceptibility of these isolates to the antiseptic agent (47 FR 22760 at 22890 to 22891). No such data were provided for phenol following the Panel's final recommendations.

The two in vivo studies were also designed following tentative guidelines (Ref. 3) under consideration by the Panel. According to those guidelines, an oral antiseptic ingredient that reduced the accumulation of dental plaque was considered to reduce microorganisms, and thus was deemed an oral antiseptic. The Panel had originally considered this in vivo method, based on plaque reduction on the teeth and periodontal tissues, as a criterion for antiseptic activity in the oral cavity, but subsequently discarded it, stating that the method was inexact and had no rational basis because dental plaque is not a disease per se (47 FR 22760 at 22840). There was considerable discussion of this issue by the Panel, and in making its final determination, the Panel relied upon the opinions of consultants and statisticians who are experts in the field, as well as on the expertise of the Panel members (47 FR 22840 to 22842). In its final report, the Panel did not accept plaque reduction as a criterion for determining effectiveness of antiseptic agents, and the agency agrees. A subsequent segment of the rulemaking for OTC oral health care drug products will cover plaque-related claims and ingredients. (See section I.M., comment 32.)

The agency disagrees with the comment that the Oral Cavity Panel arbitrarily reversed its position regarding in vitro and in vivo studies. Rather, after careful deliberations, the Panel modified its tentative in vitro guidelines, and replaced its tentative in vivo guidelines with others it believed were more appropriate. The agency believes that the Panel's proposed testing guidelines and its discussion of clinical studies represent a good starting point for the design of studies to upgrade a Category II or Category III oral antiseptic ingredient to Category I. (See section I.M., comment 33 for a further discussion of testing guidelines.) However, the agency notes that specific testing guidelines for upgrading ingredients to monograph status are not included in the tentative final monograph. (See part II. paragraph A.2.—*Testing of Category II and Category III conditions.*) All such testing should be designed using the most current technology available. The agency will meet with industry representatives or other interested parties at their request to discuss testing protocols. Any party interested in conducting studies should request a meeting at its earliest convenience.

References

(1) Comment No. C00014 and OTC Vol. 130131, Docket No. 81N–0033, Dockets Management Branch.
(2) Letter from J. D. Cope, NDMA (formerly The Proprietary Association), dated July 15, 1977, OTC Vol. 130PA3.
(3) Letter from J. D. Cope, NDMA (formerly The Proprietary Association), dated February 23, 1977, OTC Vol. 130110–B.

I. Comments on Povidone-Iodine

15. Three comments objected to the Oral Cavity Panel's conclusion that there are insufficient data available to permit classification of povidone-iodine as safe for OTC topical antimicrobial use on the mucous membranes of the mouth and throat. One comment (Ref. 1) stated that most of the safety concerns raised by the Oral Cavity Panel had been fully addressed by data submitted earlier to several other OTC drug rulemakings: (1) Topical antimicrobial drug products, (2) contraceptive and other vaginal drug products, (3) topical acne drug products, and (4) antifungal drug products. The comment contended that had the data and testimony to these other panels been considered by the Oral Cavity Panel, many safety concerns would have been resolved and duplicative efforts precluded. Another comment maintained that the Panel's conclusion that there are insufficient data available to permit classification of povidone-iodine as safe for antiseptic use on the mucous membranes of the mouth and throat is in error. A third comment mentioned that a commercially available mouthwash containing povidone-iodine has been marketed under an approved new drug application (NDA) (NDA 10–290) for a quarter century without reports of any significant adverse effects related to this product.

One comment contended that clinical and experimental studies have shown that povidone-iodine can reduce infection in wounds or surgical procedures without impairing wound healing or causing adverse reactions. The comment submitted several studies to support its statement (Refs. 2 through 9). Another comment also submitted data to establish that povidone-iodine preparations do not inhibit normal wound healing (Refs. 10, 11, and 12). The comment stated that the concern as to whether povidone-iodine accelerates or delays wound healing was addressed in detail in the Antimicrobial II Panel's report on the antifungal use of

povidone-iodine, published in the **Federal Register** of March 23, 1982 (47 FR 12480 at 12545).

One comment submitted three studies (Refs. 13, 14, and 15), one of which (Ref. 13) was also submitted by another comment, designed to demonstrate that no carcinogenic or mutagenic effects are associated with the use of povidone-iodine. Another comment submitted data regarding the capability of povidone-iodine to alter DNA in living cells. These data were also presented to the Vaginal Panel in 1978 (Refs. 15 and 16). A third comment maintained that all data relevant to the mutagenic potential of povidone-iodine had been considered by the Vaginal Panel, which concluded that povidone-iodine is not carcinogenic, teratogenic, or mutagenic. The comment submitted a review of the available data (Ref. 17).

One comment discussed the Oral Cavity Panel's statement that "chronic, indiscriminate use of PVP-I [povidone-iodine] has been associated with iodism, an increase in protein-bound iodine, and altered thyroid function," (47 FR 22760 at 22883). The comment agreed that indiscriminate use of any substance may cause harm and stated that one of the functions of proper OTC drug labeling is to instruct the consumer with appropriate directions so that indiscriminate use of pharmaceutical products can be avoided. The comment submitted FDA approved labeling (from NDA 10–290) (Ref. 18) for a commercially-available product and noted that the labeling should eliminate concerns about chronic, indiscriminate use of the product. The comment added that application of povidone-iodine to mucosal tissue does not affect normal thyroid function and stated that data had been submitted to FDA in support of this contention (Ref. 19).

One comment indicated that the Oral Cavity Panel's basis for the following statement was misdirected: "The toxic effects of PVP-I [povidone-iodine] are due to the release of free iodine and since the release occurs slowly, its toxicity and irritancy is low," (47 FR 22883). The comment agreed with the Panel that the toxicity and irritancy of povidone-iodine is low; however, the comment maintained that the low toxicity and irritancy exhibited by povidone-iodine is due to the kinetics of the available iodine dynamic equilibrium as well as the physical and chemical properties of the iodine moiety in povidone-iodine rather than the slow release of free iodine as suggested by the Panel.

One comment stated that povidone-iodine has been the subject of extensive scientific study for decades and that the medical literature contains approximately 4,000 references, including extensive long-term feeding studies in animals and humans. The comment pointed out the Oral Cavity Panel reported that povidone-iodine is nontoxic and that the free iodine released from povidone-iodine has low toxicity and irritancy (47 FR 22760 at 22883). The comment mentioned that the Panel also stated that "Povidone is practically nontoxic," "povidone is not metabolized," and "the greatest portion [of povidone] is excreted unchanged by the kidney." The comment submitted a toxicology review of data to show no biologically significant toxicity or other adverse effects of povidone-iodine following oral administration (Refs. 20 through 23). The comment contended that povidone-iodine is completely safe for use on either a short- or long-term basis.

One comment stated that the rate of absorption of povidone and iodine from the povidone-iodine complex through intact skin, vaginal mucosa, and the peritoneal cavity has been shown to be insignificant or virtually nonexistent. The comment submitted data to support its statement (Refs. 20, 24, 25, and 26). Citing "dental academicians," the comment contended that a valid comparison can be made between the histology and function of the vaginal mucosa and the oral mucosa. One comment asserted that the safety concerns raised by the Oral Cavity Panel regarding the use of povidone-iodine in the oral cavity are based upon uses of povidone-iodine solution that are not relevant to the use of low concentrations of povidone-iodine in the oral cavity. For example, the comment noted that the Panel's concern about the behavior of povidone-iodine after parenteral administration is not pertinent to the safety of oral health care drug products used topically on the mouth and throat (47 FR 22760 at 22883 to 22884). Another comment stated that because the oral mucosa and the peritoneum are very different histologically and functionally, studies on the peritoneum cited by the Oral Cavity Panel cannot be applied to the use of povidone-iodine in the oral cavity.

The agency has considered the data submitted in support of the safety of povidone-iodine, the Oral Cavity Panel's discussion of the safety of povidone-iodine (47 FR 22760 at 22883 to 22884), and the other advisory panels' evaluations of the safety of povidone-iodine. Based on this information, FDA concludes that povidone-iodine should be classified in Category I for safety as an OTC antiseptic ingredient for short-term (i.e., no more than 7 days) topical use on the mucous membrane of the mouth and throat.

As stated elsewhere in this document (see section I.A., comment 2), the agency believes that many of the oral antiseptic ingredients reviewed by the Panel, including povidone-iodine, were placed in Category III for safety because they were used commercially in mouthwashes that were recommended for long-term use on a daily basis. The agency believes that the Oral Cavity Panel's concerns regarding the safety of the long-term OTC use of oral antiseptic ingredients are not necessarily relevant to the short-term OTC use of these ingredients. In its discussion of povidone-iodine (47 FR 22760 at 22884), the Panel stated that extensive clinical observations indicated that povidone-iodine is generally nonirritating and nonsensitizing when applied to skin and mucous membranes. The Panel concluded that although povidone-iodine may be safe for occasional application to the mucous membranes, there were insufficient data to establish its safety for long-term daily use.

The Oral Cavity Panel's concern about povidone-iodine's effect on wound healing was based upon a statement in the Antimicrobial I Panel report on antimicrobial drug products published in the **Federal Register** of September 13, 1974 (39 FR 33102) that "conflicting data [had been presented] concerning the role of PVP-iodine use on the rate of wound healing." Some data presented to the Antimicrobial I Panel suggested that povidone-iodine had no effect on the rate of wound healing, while other data suggested a delay in wound healing after povidone-iodine use in animal model studies (39 FR 33102 at 33131). In its evaluation of povidone-iodine as a topical antifungal ingredient, the Antimicrobial II Panel relied on new data as well as the recommendations of the Antimicrobial I Panel. In its report, the Antimicrobial II Panel specifically addressed the effects of povidone-iodine on wound healing (47 FR 12480 at 12545), concluded that povidone-iodine has no adverse effects on wound healing, and determined that 10 percent povidone-iodine is safe for OTC use as an antifungal agent. In the tentative final monograph for OTC first aid antiseptic drug products, the agency evaluated additional new data regarding the effect of povidone-iodine on wound healing and concluded that this ingredient does not delay wound healing (56 FR 33644 at 33662). The agency has no reason to believe that the mechanism for wound healing in the oral cavity is significantly different from the mechanism for skin wound healing. Therefore, the agency

believes that the data discussed above are applicable to wound healing in the oral cavity. The agency tentatively concludes that povidone-iodine does not inhibit normal wound healing in the oral cavity.

In the tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33661 to 33662), the agency discussed data from published and unpublished studies to show that povidone-iodine does not alter thyroid function. The agency reviewed the data and agreed that thyroid disfunction does not occur from topical use of povidone-iodine. 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. The agency concluded that 0.5 to 5 percent povidone-iodine is safe for OTC use as a topical first aid antiseptic.

The agency also agrees with one comment that the currently available information indicates that povidone-iodine is not mutagenic or carcinogenic. In its evaluation of povidone-iodine as a topical antifungal ingredient, the Antimicrobial II Panel relied on new safety data as well as the recommendations of the Antimicrobial I Panel (39 FR 33102 at 33129). In its report, the Antimicrobial II Panel specifically discussed data on the mutagenicity potential of povidone-iodine (47 FR 12480 at 12545) and concluded that povidone-iodine has no significant mutagenic or carcinogenic capabilities. That Panel determined that 10 percent povidone-iodine is safe for OTC use as an antifungal agent. The Vaginal Panel reviewed a povidone-iodine migration and absorption study in three experimental animal species using radioactively tagged povidone-iodine (48 FR 46694 at 46705). Although there was evidence of absorption of iodine from the vagina into the systemic circulation, the experiments showed little or no flow of radioactively tagged povidone into the uterus from the vagina. Stating that "the weight of evidence is sufficient to conclude that povidone-iodine does not have a significant mutagenic or carcinogenic effect" (48 FR 46694 at 46705), that Panel classified povidone-iodine as Category I for the relief of minor vaginal irritations. In addition, the agency has searched the scientific literature covering 1982 through May 1993, and has not found any information indicating that povidone-iodine might be mutagenic or carcinogenic.

The agency has reviewed its adverse reaction files covering 1970 to August 1993 (Ref. 26). During those years there were no cases of adverse reactions associated with the use of povidone-iodine as an oral antiseptic. There were numerous cases of adverse reactions associated with the use of topical products containing povidone-iodine, e.g., first aid antiseptics or surgical scrubs. Of these cases, 20 were classified as serious. Five deaths occurred. However, each death occurred after the professional use of povidone-iodine as a health care antiseptic in a hospital setting (i.e., (1) use as surgical scrub on a patient who had previously been exposed to multiple radiographic examinations, (2) use to sterilize the peritoneal cavity after surgery, (3) administration concurrent with an electrolyte solution by enema and subsequently through a nasogastric tube, and (4) continuous irrigation of a hip wound). The other serious case reports involved chest pain, contact dermatitis, or chemical burns resulting from the preoperative use of povidone-iodine solutions as health-care antiseptics. These cases resulted in prolonged hospitalizations and/or disability (e.g., loss of vision or burns of varying degrees). The most frequently reported events included: reports of rash, reports of contact dermatitis, reports of application site reactions, reports of vaginitis, and reports of pain. Other less frequently reported reactions (i.e., 1 or 2 reports per reaction) included conjunctivitis, anaphylactic shock, iodism, rhinitis, and dry skin. The agency notes that the majority of these cases were the result of povidone-iodine products being used by health care professionals on people who were in the hospital for surgery or who were otherwise compromised. In addition, the povidone-iodine concentration in the products used in these cases was 5 to 10 percent, which is much higher than its concentration in oral antiseptic products (0.5 percent). The agency does not believe that these reports are relevant to the use of povidone-iodine as an oral antiseptic product used in small amounts in the oral cavity for a limited period of time (i.e., up to 7 days).

The agency believes that the information contained in its adverse reaction files and the safety data evaluated by the Oral Cavity Panel are sufficient to conclude that 0.5 percent povidone-iodine (i.e., the concentration evaluated by the Oral Cavity Panel) is safe as an OTC oral antiseptic for short-term use (not to exceed 7 days).

References

(1) Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(2) Bradley, S. G., "A Review on Some Microbiological Aspects of Povidone-Iodine (PVP-I)," Addendum 20, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(3) Prince, H. N. et al., "Drug Resistance Studies with Topical Antiseptics," *Journal of Pharmaceutical Sciences*, 67:1629–1630, 1973.

(4) Eitzen, H. E., "Efficacy of Povidone-Iodine (PVP-I)," Addendum 22, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

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

(6) Eitzen, H. E. et al. "A Microbiological In-Use Comparison of Surgical Hand-Washing Agents," *The Journal of Bone and Joint Surgery, Incorporated*, 61–A:403–406, 1979.

(7) Steere, A. C., and G. F. Mallison, "Handwashing Practices for the Prevention of Nosocomial Infections," *Annals of Internal Medicine*, 83:683–690, 1975.

(8) Morgan, W. J., "Povidone-Iodine Spray for Wounds Sutured the Accident Department," Addendum 26, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(9) Carchman, R. A., "The Effects of Povidone-Iodine on Wound Healing," Addendum 27, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(10) Fischer, E., and Z. Paster, "A Study of the Effect of Polydine on Wound Healing," Appendix 10, Comment No. C00019, Docket No. 81N–0033, Dockets Management Branch.

(11) 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.

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

(13) Schwartz, S. L., "Evaluation of the Safety of Povidone and Crospovidone," Addendum 16, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(14) "Studies on Testing of Povidone-Iodine U.S.P. XIX for Mutagenic Effects in Mice and Chinese Hamsters," Comment No. C00019, Docket No. 81N–0033, Dockets Management Branch.

(15) Merkle, J., and H. Zeller, "Absence of Povidone-Iodine-Induced Mutagenicity in Mice and Hamsters," *Journal of Pharmaceutical Sciences*, 68:100–102, 1979.

(16) Kessler, F. K. et al., "Assessment of Somatogenotoxicity of Povidone-Iodine Using Two In Vitro Assays," Addendum 15, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(17) Brusick, D. J., "A Review of the Genotoxic Effects of Povidone-Iodine," Attachment B, Comment No. C00010, Docket No. 81N–0033, Dockets Management Branch.

(18) Attachment A, Comment No. C00010, Docket No. 81N–0033, Dockets Management Branch.

(19) "Serum Fodides and Thyroid Function; Betadine Mouthwash/Gargle (Povidone-Iodine)," Attachment C, Comment No. C00010, Docket No. 81N–0033, Dockets Management Branch.

(20) Borzelleca, J. F., "A Review of the Basic Toxicology of Povidone-Iodine," Addendum 4, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(21) "Toxicology Summary of PVP," Addendum 17, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(22) Blecher, L. et al., "Polyvinylpyrrolidone," Addendum 18, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(23) Digenis, G. A., "Behavior of Povidone-Iodine in the Vaginal Vault of the Rat, Dog, and Sheep," Addendum 11, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(24) Istin, M., "Study of the Urinary, Biliary, and Fecal Excretion of C^{14} by Rats Treated with Labeled Polyvinylpolypyrrolidone (PVPP–C^{14}) by Gastric Intubation," Addendum 12, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(25) Ingbar, S. H., "Studies of the Effects of Surgical Scrubbing with PVP–I," Addendum 13, Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(26) Food and Drug Administration, Center for Drug Evaluation and Research, Adverse Reaction Summary Listing for Povidone-iodine for the years 1970 to August 1993, OTC Vol. 13CTFM, Docket No. 81N–0033, Dockets Management Branch.

16. Two comments objected to the Oral Cavity Panel's conclusion that there is insufficient evidence available to classify povidone-iodine in Category as an effective oral antiseptic. One comment stated that a commercial mouthwash has been marketed under an approved NDA for a quarter century and that reports of clinical studies involving thousands of patients had been submitted to the Panel.

The comments objected to the Panel's statement that the "* * * slow release [of povidone-iodine] also raises doubts about its effectiveness, since the active ingredient is elemental iodine," (47 FR 22760 at 22883). One comment stated that the Panel's speculation on the release of iodine and its impact on the effectiveness of povidone-iodine is unfounded. The comment added that the effectiveness of povidone-iodine solution as a topical microbicide is proven in the hundreds of studies submitted or referenced to the Panel. The comment contended that the Panel did not develop an independent viewpoint regarding the effectiveness of povidone-iodine but relied upon the Antimicrobial I Panel's evaluation. The comment argued that the issues raised by the Antimicrobial I Panel were fully answered by the data submitted in response to that Panel's report.

Another comment stated that the efficacy of the povidone-iodine complex is independent of the initial content of free iodine and that biocidal effect is determined by iodine liberated from the complex during the reaction with amino acids of the proteins of bacteria, fungi, etc. The comment mentioned that substantial data submissions to the Antimicrobial I Panel and other panels showed that iodine is freely released from the complex and that the rate of iodine release is controlled by tissue demand. The comment submitted data regarding the rate of release and germicidal activity of povidone-iodine (Refs. 1, 2, and 3). The comment stated that the studies established that: (1) The biocidal activity of the complex is independent of the initial free iodine content; (2) the clinical effectiveness of the complex is caused by the amount of available iodine; (3) the iodine becomes effective by oxidation or iodizing reaction of amino acids of the proteins of bacteria, fungi, etc.; (4) the iodine is liberated from the povidone-iodine complex at a rate in the milliseconds time range; and (5) within the acidity levels studied (i.e., those levels relevant to the field of medicine, between pH 3 and 5), no significant change with regard to the rapidity of iodine release from the povidone-iodine complex could be observed. The comment concluded that there are sufficient data available to establish the effectiveness of povidone-iodine for use as an OTC oral antiseptic.

As part of FDA's DESI program, mouthwash products containing povidone-iodine, cetylpyridinium chloride, and other ingredients were reviewed by the NAS-NRC/DESC and found ineffective for claims relating to antimicrobial, antiseptic, germicidal, and analgesic uses (35 FR 12423). In a subsequent notice published in the **Federal Register** of December 2, 1971 (36 FR 23000), the agency stated that because of the implementation of the OTC drug review, mouthwash and gargle products reviewed under the DESI program would now be under the purview of the OTC drug review; thus, final agency action on these products would be deferred pending evaluation of the data and information concerning such products under the OTC drug review.

The agency has reviewed the data submitted regarding the availability of iodine from the povidone-iodine complex and considered the data discussed in the tentative final monograph for OTC topical acne drug products, published in the **Federal Register** of January 15, 1985 (50 FR 2172 at 2173 to 2174) and in the tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33661). The agency agrees with the comment that the issues regarding the availability of iodine from povidone-iodine complex and the stability of the complex have been resolved for this ingredient. However, the agency has determined that further studies are needed to demonstrate the effectiveness of povidone-iodine for OTC topical use in the oral cavity to help prevent infection.

As discussed in section I.K., comment 27, the agency believes that 0.5 percent povidone-iodine is an effective oral antiseptic for professional use when used for the preparation of the oral mucosa prior to injection, dental surgery, or tooth extraction by a health care professional. However, the data discussed in that comment do not support OTC use of povidone-iodine as an OTC oral antiseptic. The data demonstrate that applying povidone-iodine according to the specialized professional labeling directions proposed in § 356.80(c)(3) of this tentative final monograph results in a decrease of bacteremia after oral surgery or tooth extraction. They did not demonstrate a therapeutic benefit from using povidone-iodine as an OTC oral rinse. Although the gingival mucosa surrounding the operation sites were sampled prior to and immediately after surgery or tooth extraction, the studies did not demonstrate a decrease in the number of oral bacteria over an extended period of time, and the organisms affected by the povidone-iodine treatment were not completely identified. These studies do not demonstrate the effectiveness of povidone-iodine when used as an OTC oral rinse. In addition, the agency is not aware of any data from clinical studies demonstrating a therapeutic benefit from the OTC use of povidone-iodine in the oral cavity.

The agency believes that the Panel's proposed in vitro and in vivo testing guidelines and its discussion of clinical studies represent a good starting point for the design of studies to upgrade a Category II or Category III oral antiseptic ingredient to Category I. (See section I.M., comment 33 for a further discussion of testing guidelines.) However, the agency notes that specific testing guidelines for upgrading ingredients to monograph status are not included in this monograph. (See part II. paragraph A.2.—*Testing of Category II and Category III conditions.*) All such testing should be designed using the most current technology available. The agency will meet with industry representatives or other interested parties at their request to discuss testing protocols.

References

(1) Appendix 2, Comment No. C00019, Docket No. 81N–0033, Dockets Management Branch.

(2) Appendix 3, Comment No. C00019, Docket No. 81N–0033, Dockets Management Branch.

(3) Appendix 4, Comment No. C00019, Docket No. 81N–0033, Dockets Management Branch.

17. One comment objected to the Oral Cavity Panel's statement (47 FR 22760 at 22882) that "There is some disagreement concerning the chemical nature of povidone-iodine. Some believe that it is a specific chemical entity; others claim that it is merely a complex. The prevalent consensus is that povidone-iodine is a complex of povidone and elemental iodine." Maintaining that there is no disagreement among qualified scientists concerning the chemical nature of povidone-iodine, the comment stated that povidone-iodine is a specific chemical entity that is defined in the Official Compendia and the scientific literature. Referring to the "United States Pharmacopeia (U.S.P.) XX" description of povidone-iodine as "* * * a complex of iodine with povidone" (Ref. 1), the comment contended that the fact that povidone-iodine is described as a complex does not contradict its existence as a chemical entity. The comment stated that a "complex" is formed by the "bonding of two or more compounds, resulting in a new chemical entity having properties distinguishable from those of the component parts." According to the comment, data in the public record demonstrate that povidone-iodine is a well-defined chemical entity that retains the full antimicrobial spectrum of iodine without the noxious chemical and physical properties of elemental iodine, thereby providing a stable, essentially nonirritating and nontoxic compound.

Another comment agreed with the Oral Cavity Panel's recognition of the "prevailing consensus" that povidone-iodine is a complex composed of povidone and iodine. However, this comment felt that the Panel may have been unaware of the nature of povidone-iodine, and contended that this lack of awareness may have affected other considerations concerning the source of the complex's effectiveness, the rate of iodine release, and the complex's effect on the rate of healing. The comment included a detailed chemical description of povidone-iodine and of povidone-iodine's activity (Ref. 2).

One comment asserted that the Panel's misunderstanding of the nature of povidone-iodine is indicated by its statement that "Povidone is available as a series of aggregates having mean molecular weights ranging from 10,000 to 700,000 daltons," (47 FR 22760 at 22883). Stating that the U.S.P. XX described povidone as a series of products rather than a series of aggregates (Ref. 1), the comment maintained that the povidone product used in the synthesis of povidone-iodine does not spread over the broad range of molecular weights described by the Panel but has a molecular weight average of less than 40,000. The comment added that this specificity in molecular weight must be recognized when considering the properties of the povidone used to synthesize povidone-iodine.

The agency has reviewed the literature and believes that povidone-iodine is a well-defined chemical. Povidone-iodine is described in "U.S.P. XXII" (Ref. 3) and in "Martindale, The Extra Pharmacopeia" (Ref. 4) as a complex of iodine with povidone (2-pyrrolidinone, 1-ethenyl-, homopolymer or 1-vinyl-2-pyrrolidinone polymer) that contains not less than 9 percent and not more than 12 percent of available iodine calculated on a dried basis. "U.S.P. XXII" (Ref. 3) provides standards for the purity and acceptability of iodine, povidone, and povidone-iodine. Other references describe povidone-iodine as iodine compounded or complexed with povidone (Refs. 5 and 6).

Regarding the Panel's statement that "Povidone is * * * a series of aggregates * * *" (47 FR 22760 at 22883), the agency notes that "U.S.P. XXII" describes povidones as a "synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups, the degree of polymerization of which results in polymers of various molecular weights," (Ref. 3). Povidone is produced commercially as a series of products having mean molecular weights ranging from about 10,000 to about 700,000 (Ref. 6), and the Panel correctly described the range of molecular weights of povidone available. However, it neglected to point out that povidone having an average molecular weight of 40,000 is used in the preparation of povidone-iodine (Ref. 6). For the above reasons, the agency concludes that there is little or no disagreement regarding the chemical nature of povidone-iodine.

References

(1) "The United States Pharmacopeia XX," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 647, 1980.

(2) Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(3) "The United States Pharmacopeia XXII—The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 1118–1119, 1989.

(4) Reynolds, J. E., editor, "Martindale, The Extra Pharmacopoeia," 29th ed., The Pharmaceutical Press, London, p. 1187, 1989.

(5) Gardner, W., E. I. Cooke, and R. W. I. Cooke, "Handbook of Chemical Synonyms and Trade Names," CRC Press, Inc., Cleveland, p. 576, 1978.

(6) Gennaro, A. R., editor, "Remington's Pharmaceutical Sciences," 18th ed., Mack Publishing Co., Easton, PA, pp. 1169 and 1307, 1990.

18. Two comments maintained that several of the Oral Cavity Panel's statements in its discussion of povidone-iodine (47 FR 22760 at 22882 to 22885) showed a basic misunderstanding of the behavior of povidone-iodine in solution. One comment requested that the Panel's introductory discussion of povidone-iodine be rewritten to properly reflect the chemical and physical properties of povidone-iodine and that the information provided should accurately describe the product used in the formulation of OTC oral health care antimicrobial preparations.

The comment asserted that the Panel's statement which reads "The iodine that can be released in its free form from povidone-iodine is approximately 10 percent of the labeled iodine content of the complex" (47 FR 22883) is misleading. The comment noted that povidone-iodine powder contains about 10 percent available iodine and a 10-percent aqueous solution of povidone-iodine provides 1 percent titratable iodine, all of which is available for germicidal use.

The comment indicated that the following statement made by the Panel is in error: "Freshly prepared solutions of povidone-iodine do not give a blue color with starch as do tinctures and other solutions of elemental iodine. Solutions that have been standing for some time do give a blue color" (47 FR 22883). The comment referred to the two identification tests required by the U.S.P. for povidone-iodine solution (Ref. 1) and stated that identification test A requires a blue color upon mixture of a povidone-iodine solution with starch TS (test solution), and test B requires that no blue color be produced. Stating that test B detects the presence of uncomplexed free iodine, the comment asserted that properly manufactured povidone-iodine solutions conform to these U.S.P. standards and do not deteriorate and release free iodine vapor under normal storage conditions, as the Panel's quoted statement implies.

The comment objected to the following statement in the Panel's discussion of povidone-iodine: "The

addition of sodium bicarbonate makes aqueous solutions less acidic, but also less stable," (47 FR 22760 at 22883), and noted that "a current In-Process Revision of the U.S.P." provides for a pH range of 2.0 to 6.5. Citing the "Pharmacopeial Forum" (Ref. 2), the comment stated that this pH range reflects the range of values found in commercial formulations and is consistent with adequate stability, germicidal activity, and dermal safety. Noting that product stability is fully regulated under Current Good Manufacturing Practice (CGMP) regulations found in 21 CFR parts 210 and 211, the comment maintained that its povidone-iodine mouthwash gargle product is stable, has a documented shelf-life stability, and is labeled with an expiration date.

Citing the Panel's statement "When an aqueous solution is applied topically, a slow release of free iodine occurs which exerts antimicrobial action" (47 FR 22760 at 22883), the comment asserted that the activity of povidone-iodine solution is not the result of a slow, "trickle type" of release of free iodine, but occurs because iodine is available in the course of a continuous, dynamic equilibrium reaction. The comment added that the dynamic equilibrium results in the immediate availability of all the iodine present in the solution at virtually the same rate as for tincture of iodine. The comment maintained that data submitted to the Oral Cavity Panel, the Antimicrobial I Panel, and the rulemaking for OTC topical acne drug products demonstrate that all of the iodine present in an aqueous solution of povidone-iodine is instantly (i.e., within milliseconds) available upon application to the tissue site; therefore, the Panel's reference to a "slow release of free iodine" is incorrect.

The second comment maintained that a key factor in the availability of elemental iodine from the povidone-iodine complex is the ability of the complex to keep the antimicrobial iodine in reserve and supply it only on demand. The comment stated that when there is no iodine demand, the level of free iodine is kept quite low, contrary to the Panel's statement regarding the continuous "slow-release" of iodine. The comment contended that at equilibrium the concentration of iodine is low, but as the iodine is depleted from the solution, it is replaced instantaneously from the available pool. Thus, the comment concluded that the rate of release of iodine is not variable, but is always the same and that the germicidal activity of povidone-iodine is not affected until the entire pool is depleted. The comment submitted data describing the structure and the kinetics of iodine release from the povidone-iodine complex (Refs. 3 and 4) and purporting to confirm the in vitro microbiological consequences of the release mechanism (Ref. 5).

The agency considers the following statement made by the Panel in its discussion of povidone-iodine to be unclear and undocumented: "Freshly prepared solutions * * * do not give a blue color * * *" (47 FR 22760 at 22883). The agency agrees with the comments that properly manufactured povidone-iodine solution must comply with the appropriate U.S.P. standards that include two identification tests: one in which the formation of a blue color confirms the presence of available iodine in the povidone-iodine solution, and the other in which the lack of a blue color confirms that free iodine is not being released into the atmosphere (Ref. 6). The absence of free iodine in the atmosphere is indicative that the vapor pressure of povidone-iodine solution is virtually zero in contrast to the high vapor pressure demonstrated by iodine tincture.

Regarding the Panel's statement that "The addition of sodium bicarbonate makes aqueous solutions [pH 2.0] less acidic, but also less stable" (47 FR 22760 at 22883), the agency notes that the U.S.P. specifies a pH range between 1.5 and 6.5 for povidone-iodine topical solutions (Ref. 6). Therefore, a povidone-iodine topical solution should be stable for its shelf life at any pH between 1.5 and 6.5. The agency also agrees with the comment that issues regarding stability would be governed by the CGMP regulations (21 CFR parts 210 and 211). These regulations require a written testing program to assess the stability of finished products and to determine appropriate storage conditions and an expiration date. Section 211.137(a) (21 CFR 211.137(a)) requires that products bear an expiration date supported by appropriate stability testing. However, § 211.137(g) provides that expiration dating requirements are not enforced for human OTC drug products if their labeling does not bear dosage limitations and they have been shown to be stable for at least 3 years by appropriate stability data.

The agency has reviewed the data submitted on the kinetics of iodine released from the povidone-iodine complex in solution (Refs. 3 and 4) and discussed the data in the tentative final monograph for OTC topical acne drug products (50 FR 2172 at 2173 and 2174) and in the tentative final monograph for OTC topical antifungal drug products published in the **Federal Register** of December 12, 1989 (54 FR 51136 at 51143 and 51144). The agency agrees with the comment that all of the iodine in a povidone-iodine solution is immediately available and that the rate of iodine release from the povidone-iodine complex is neither slow nor variable.

Regarding the comment's statement that povidone-iodine powder contains 10 percent available iodine and that a 10-percent solution of povidone-iodine contains 1 percent available iodine, the agency notes that "U.S.P. XXII" states that povidone-iodine powder contains not less than 9 percent and not more than 12 percent available iodine (Ref. 6). Earlier compendia (e.g., "U.S.P. XIX" (Ref. 7)) characterized a 10-percent povidone-iodine solution as equivalent to 1 percent available iodine.

Regarding the data submitted to confirm the in vitro microbiological consequences of the povidone-iodine complex's release mechanism (Ref. 5), the agency discusses the oral antimicrobial effectiveness of povidone-iodine in section I.I., comment 16.

One comment requested that the introductory portion on povidone-iodine in the Panel's report should be rewritten to reflect these corrections. Although the agency acknowledges some ambiguities in the Panel's introductory discussion of povidone-iodine (47 FR 22760 at 22882 to 22885), it does not see a need to rewrite that discussion. The agency believes that the above response should add to and clarify the Panel's discussion of the chemical and physical nature of povidone-iodine in solution.

References

(1) Comment No. C00010, Docket No. 81N–0033, Dockets Management Branch.

(2) "Pharmacopeial Forum," The United States Pharmacopeial Convention, Inc., Rockville, MD, p. 2343, September and October, 1982.

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

(4) 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," in Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(5) Marcus Research Laboratory Inc., Chemists, "Povidone-Iodine U.S.P., Chemistry, Microbiology, and Toxicology," in Comment No. C00020, Docket No. 81N–0033, Dockets Management Branch.

(6) "United States Pharmacopeia XXII–The National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 1119, 1989.

(7) "United States Pharmacopeia XIX," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 396, 1975.

J. Comments on Dosages for Oral Antiseptic Ingredients

19. One comment stated that the dosage level of 0.025 percent eucalyptol, as recommended in the Oral Cavity Panel's majority report on antimicrobial agents (47 FR 22760 at 22873), is incomplete. The comment contended that the dosage should read 0.025 to 0.1 percent concentration, the range reviewed by the Panel and correctly listed in the Panel's evaluation of eucalyptol as an anesthetic/analgesic (47 FR 22827).

The agency has reviewed the administrative record regarding the Panel's evaluation of eucalyptol as an antimicrobial agent and notes that one product submitted to the Panel contained eucalyptol at a concentration of 0.025 percent (Ref. 1), while another submitted product contained 0.091 percent eucalyptol (Ref. 2). The Panel also reviewed data on products containing eucalyptol used as an anesthetic/analgesic ingredient in the same dosage range (i.e., 0.025 to 0.091 percent) and apparently rounded off the 0.091 percent dose in the data to 0.1 percent in its report. Therefore, the agency agrees with the comment that the proposed dosage range for eucalyptol as an antiseptic agent should also have read 0.025 to 0.1 percent. However, because eucalyptol is classified as Category III as both an oral health care antiseptic and anesthetic/analgesic ingredient in the OTC oral health care drug products rulemaking, the proposed dosage range serves only as a guide to anyone interested in testing eucalyptol for upgrading to Category I. However, data on any concentration of eucalyptol may be submitted.

References

(1) OTC Vol. 130053.
(2) OTC Vol. 130042.

K. Comments on Labeling for Oral Antiseptic Ingredients

20. Three comments objected to the Oral Cavity Panel's recommendation that the term "antiseptic" and any reference to the pharmacologic effects of antimicrobial agents not be included in its recommended monograph. One comment stated that the Panel's position is contrary to the act, which requires a statement of pharmacologic effect or class of drug in OTC labeling. Another comment contended that the term "antiseptic" should be preserved in the statement of identity because, by traditional definition, an antiseptic is a substance that kills or inhibits the growth of microorganisms. Stating that antiseptic activity is synonymous with antimicrobial activity, the comment requested the approval of the following terms as statements of identity for OTC oral antimicrobials: (1) Oral antimicrobial, (2) oral antiseptic, and (3) oral antibacterial. The other comment added that the terms "antiseptic" and "kills germs" should be placed in Category I in the tentative final monograph.

In discussing the use of the terms "antiseptic," "disinfectant," and "antimicrobial agent," the Oral Cavity Panel stated that the term "antimicrobial agent" describes an ingredient in OTC oral health care drug products that kills or interferes with the proliferation and activity of microorganisms, both pathogenic or nonpathogenic, and that a therapeutic benefit may or may not be derived from its use (47 FR 22760 at 22833). The Panel defined the term "antiseptic" as an antimicrobial agent that, when used on living tissue, produces some therapeutic benefit and acts to counteract an infection. A "disinfectant" was defined as an antimicrobial agent used on inanimate objects. Thus, the Panel considered the term "antimicrobial agent" to be a general term that encompasses both antiseptics and disinfectants, disregarding how the ingredient is used. The Panel included the following statement of identity in § 356.51(a) of its recommended monograph (47 FR 22760 at 22928): "oral health care antimicrobial."

The agency disagrees with the Panel's recommendation that the term "antiseptic" not be used as part of the statement of identity for antimicrobial agents contained in OTC oral health care drug products (47 FR 22760 at 22833). The agency believes that the Panel was opposed to the term "antiseptic" because, according to the Panel's definition, this term implies therapeutic benefit and the Panel was not convinced of the effectiveness of OTC antiseptics in providing a therapeutic benefit, i.e., relief of sore mouth and sore throat symptoms. However, the agency believes that the term "oral antiseptic" is appropriate for use in the statement of identity for the active ingredients included in this segment of the oral health care drug products rulemaking. Those found effective could provide a therapeutic benefit. An antiseptic is a substance that can kill or inhibit the growth of microorganisms when applied to living tissues without significant harm to the tissues (Ref. 1). This definition is in keeping with the definition of an antiseptic in section 201(o) of the act (21 U.S.C. 321(o)). If safety and effectiveness data support the inclusion in Category I of any antiseptic active ingredient(s) for OTC use in oral health care drug products, the agency believes that the term "antiseptic" is well recognized by consumers and can appropriately be used in the labeling for such products.

The agency believes that the term "health care," while appropriate for classification purposes and used to identify this rulemaking, is cumbersome and unnecessary in consumer labeling as a statement of identity for an OTC oral antiseptic. Therefore, in this tentative final monograph, the agency is proposing to revise the statement of identity in § 356.51(a) of the Panel's recommended monograph (47 FR 22928) to include the term "antiseptic" instead of the term "health care antimicrobial." The agency is also revising the statement of identity to include dosage forms (see section I.K., comment 21), and is renumbering the statement of identity section as § 356.64(a).

Because the term "antiseptic" is well recognized by consumers and because the agency wishes to minimize consumer confusion about the labeling of similar marketed products, the terms "oral antimicrobial" and "oral antibacterial" are not being included as alternate statements of identity for this class of drug products. However, the agency has no objection to such terms appearing in the labeling as other information provided it does not appear in any portion of the labeling required by the monograph and does not detract from such required information.

The agency is not including in this tentative final monograph the Panel's definition for an antimicrobial agent in § 356.3(c) of its recommended monograph (47 FR 22760 at 22927). Instead, the agency is proposing definitions for the terms "antiseptic drug" and "oral antiseptic" in § 356.3 as follows:

Antiseptic drug. In accordance with section 201(o) of the Federal Food, Drug, and Cosmetic 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."

Oral antiseptic. An antiseptic-containing drug product applied topically to the oral cavity to help prevent infection in wounds caused by minor oral irritations, cuts,

scrapes, or injury following minor dental procedures.

The agency believes that claims such as "kills germs" could be potentially misleading to the average consumer if directly associated with the term "infection" that is included in the indication. The term "kill germs" may be interpreted to imply elimination of all bacteria in the mouth when, in fact, oral antiseptics used in the mouth only decrease the number of certain bacteria. However, the agency believes this term is familiar to the average consumer and may be useful in describing a product's action or intended effect. Although this term is not included in the monograph, it may be included in labeling of oral antiseptic drug products provided it is not intermingled with labeling established by the monograph and is not used in a false or misleading manner.

Reference

(1) Berkow, R., editor, "The Merck Manual of Diagnosis and Therapy," 14th ed., Merck and Co., Inc., Rahway, NJ, p. 2300, 1982.

21. One comment requested that the agency approve the following statements of identity, and any reasonably synonymous statements, for the combination of 0.045 percent cetylpyridinium chloride and 0.005 percent domiphen bromide: "(1) oral antiseptic, (2) oral antimicrobial, (3) mouthwash, (4) gargle, and (5) mouthwash and gargle."

The statement of identity for oral health care antiseptics is discussed in section I.K., comments 20 and 22. As explained there, the agency believes that the term "oral antiseptic" is appropriate as the statement of identity for these products. Because the term "antiseptic" is well recognized by consumers, and in order to avoid confusion in the marketplace, the term "oral antimicrobial" is not being included in the monograph as an alternate statement of identity. However, the agency has no objection to the term "oral antimicrobial" appearing in the labeling as other information provided it is not intermingled with labeling established by the monograph, and it is not used in a false or misleading manner.

In accord with 21 CFR 201.61, wherever possible, the agency prefers to use the general pharmacological category as the statement of identity for OTC drug products; where this is not appropriate, the principal intended action is used. The terms "mouthwash," "gargle," or "mouthwash and gargle" by themselves do not inform consumers of the pharmacological category or the principal intended action of a drug product. The agency recognizes that oral products have been marketed for years as "mouthwashes," "gargles," and "mouthwashes and gargles." However, many of these products have been marketed for daily long-term use as cosmetics, and the agency believes that consumers associate the term mouthwash with such unlimited cosmetic use. In this document, the agency is proposing to limit the use of oral antiseptic drug products to 7 days or less. The agency believes that use of the term "mouthwash" on such products could be confusing to consumers, who might be led to assume that the product could be used for an unlimited period of time. However, the agency believes that use of the term "rinse" in the statement of identity would be acceptable because the term "rinse" implies a therapeutic use (e.g., fluoride rinse). Also, the agency does not oppose the inclusion of the term "gargle" in the statement of identity, when included in addition to the required pharmacological category. Therefore, in this tentative final monograph, the agency is proposing an alternate statement of identity for oral antiseptics to include a choice of terms describing the appropriate dosage form of the product, i.e., "rinse," "gargle," or "rinse and gargle," as follows: The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral antiseptic," or an "antiseptic" (select one of the following: "rinse," "gargle," or "rinse and gargle"). (See section I.K., comment 20.)

In this tentative final monograph, the agency is classifying cetylpyridinium chloride, domiphen bromide, and a combination of cetylpyridinium chloride and domiphen bromide in Category III for effectiveness as oral health care antiseptics. (See section I.E., comment 9; section I.G., comment 13; and section I.L., comments 30 and 31.) If cetylpyridinium chloride, domiphen bromide, or a combination of these ingredients are upgraded to Category I for OTC oral antiseptic use, the product may be labeled with either statement of identity proposed in § 356.64(a) of this tentative final monograph.

22. Four comments objected to the Oral Cavity Panel's position that antimicrobial agents should not be used for therapeutic purposes in OTC oral health care products. Three of the comments disagreed with the Panel's statement that antiseptics are used in an attempt to sterilize intact cutaneous and mucous surfaces, contaminated or infected wounds, mucosal ulcerations, or other lesions caused by pathogenic microbial activity (47 FR 22760 at 22831). The comments pointed out that topical antimicrobials are used to decrease the number of bacteria present and to help prevent the chance of infection after minor injury to the mouth or gums; they are not used as sterilizing agents. The comments presented excerpts from the advance notice of proposed rulemaking on alcohol drug products for topical antimicrobial OTC human use published in the **Federal Register** of May 21, 1982 (47 FR 22324) and the tentative final monograph on OTC topical antibiotic drug products published in the **Federal Register** of July 9, 1982 (47 FR 29986) which, they stated, show that the Miscellaneous External Panel and the agency, respectively, favor the use of antimicrobial agents to reduce the number of bacteria on the skin and thus help prevent infection. One of the comments also pointed out that the Oral Cavity Panel's position is directly contrary to that of the Dental Panel which found that the use of an oral antimicrobial is rational therapy (47 FR 22712 at 22720).

One comment noted that the Oral Cavity Panel identified and evaluated two categories of products containing antimicrobial active ingredients: (1) Those used on a short-term basis to relieve symptoms of sore mouth or sore throat, or both, due to microbial infections, and (2) those used on a long-term, often day-to-day, basis. The comment contended that the category of products used on a short-term basis should be further divided into two groups: (1) Products used on a short-term basis that are applied locally (i.e., to the affected site of infection to reduce the number of bacteria), and (2) products used on a short-term basis that are applied to the total oral cavity.

Stating that presentations had been made to the Oral Cavity Panel concerning the existence of a target population for locally applied topical antiseptics, the comment felt that the data supplied on the historical use of topical antiseptics to assist in preventing infection were adequate to establish an oral first aid antiseptic category (Ref. 1). The comment stated that the only indication provided by the Panel for any OTC oral antimicrobial ingredient does not address the issue of reducing organisms at the lesion or site of infection to help prevent oral infection, i.e., the "first aid" category. The comment requested that the following indication and other allowable indications be included as Category I labeling:

Indication: First aid and/or antiseptic to help prevent infection in wounds caused by minor oral irritation; cuts, scrapes or injury

such as following minor dental procedures or from dentures and orthodontic appliances.

Other Allowable Indications: (i) "Decreases" or "Helps" reduce the number of bacteria on the treated area.

(ii) Helps "prevent," "guard against," or "protect against" oral infections.

(iii) Helps reduce the "risk" or "chance" of oral infection.

(iv) Helps prevent bacterial contamination in minor injuries or lesions of the mouth.

The comment also requested that, based upon available data, carbamide peroxide in anhydrous glycerin, sodium phenolate and phenol, and povidone-iodine be classified in Category I as topical antiseptics for local application.

Regarding the Oral Cavity Panel's statement that antiseptics are used in an attempt to sterilize surfaces, wounds, and lesions caused by pathogenic microbial activity (47 FR 22760 at 22831), the agency agrees with the comments that most of the antiseptic agents used in OTC health care drug products are not effective as sterilizing agents. For an antiseptic agent to be an effective sterilizing agent, the ingredient must be sporicidal, i.e., must kill bacterial spores. The majority of the antiseptics used in OTC oral health care products will not destroy bacterial spores. However, as the Panel stated, "Topical antimicrobial ingredients are applied to the mucous membranes of the mouth and throat to kill, inhibit the proliferation of, or alter the metabolic activity of all types of microorganisms, both pathogenic and nonpathogenic," (47 FR 22760 at 22831). The antiseptics are used in an "attempt to sterilize" intact surfaces with complete sterilization of the wound site viewed as the ultimate achievement by the drug. In an ideal sense, a drug that could sterilize a wound site would be very beneficial in the treatment of cuts and scratches. The agency believes that is the point the Panel was trying to relate in its description of the effects of these drugs.

The agency notes that the Panel listed nine reasons why it believed that antiseptic ingredients should not be used in OTC oral health care drug products (47 FR 22760 at 22834). Most of the reasons were based on the Panel's belief that: (1) Antiseptics are nonspecific ingredients that would not be effective in treating wounds in the oral cavity and could possibly be harmful, (2) these ingredients do not penetrate deeply into tissue, and (3) the ingredients would be significantly diluted and removed from the wound site by the action of saliva. Therefore, the Panel did not recommend any Category I indications for antiseptics, but instead included a Category III indication, "For the temporary relief of minor sore mouth and sore throat by decreasing the germs in the mouth." However, the agency disagrees with the Panel's position that antiseptic ingredients should not be used for other therapeutic purposes in OTC oral health care drug products. The agency believes that antiseptics may be useful in helping to reduce the chance of infection in minor sore mouth conditions by decreasing the number of bacteria on the mucous membranes of the mouth.

Two of the studies submitted by one comment provide support that there is a target population that would benefit from the availability of an OTC antiseptic drug product to help prevent or reduce the incidence of certain oral conditions (Ref. 1). Addy et al. (Ref. 2) reported that an antibacterial mouthwash (0.2 percent chlorhexidine gluconate) reduced the incidence, duration, and severity of aphthous ulcers (canker sores) as compared to a control and an astringent mouthwash when evaluated subjectively. The mouthwash was used for 1 minute three times daily for a period of 5 weeks. The authors speculated that, in such conditions, oral hygiene is frequently neglected due to oral discomfort that further increases the possibility of infection from bacterial plaque deposits. Thus, attempts to reduce secondary infection of the aphthous ulcers may be of value for the patient. Olsen (Ref. 3) evaluated patients with denture stomatitis. The treatment consisted of each patient sucking placebo, amphotericin B, or chlorhexidine chloride lozenges combined with denture soaking in a 0.2-percent aqueous solution of chlorhexidine digluconate. Olsen concluded that denture disinfection was an essential part in the management of denture stomatitis, finding that denture immersion in 0.2 percent chlorhexidine solution significantly reduced the number of organisms both on the mucous membranes and on the denture. The combination of amphotericin B lozenges and chlorhexidine denture disinfection was the most effective regimen. Although chlorhexidine, a drug available by prescription for oral use, was used in the studies, the agency believes that these studies do support the existence of a target population that would benefit from the use of antiseptic ingredients in helping to alleviate some oral conditions. However, additional data are needed to support the above indications for OTC oral antiseptics.

The Panel identified two categories of products containing antiseptics for oral use: (1) Those used on a short-term basis to relieve symptoms of sore mouth and sore throat, or both, due to microbial infections, and (2) those used on a long-term, often day-to-day, basis for cleansing the mouth, suppressing mouth odors, and other related purposes in which no symptoms of an infectious process are evident but for which antiseptic claims are made (47 FR 22760 at 22890).

The agency does not see a need at this time to follow one comment's request to subdivide the category of OTC oral antiseptic products used on a short-term basis into two groups: (1) Those applied locally, and (2) those applied to the total oral cavity. The agency believes that on a short-term basis antiseptic ingredients can be used for local application or for application to the total oral cavity to help prevent infection in minor sore mouth conditions. Other monographs, e.g., the tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33677) and the amendment to the tentative final monograph for OTC oral health care drug products (56 FR 48302 at 48343 to 48346), identify situations where short-term use of a product for minor sore mouth conditions is appropriate for consumer selfmedication (e.g., use in minor oral wounds, accidental injury or irritation of the mouth or gums, or minor wounds resulting from orthodontic appliances or dentures). Accordingly, the agency is proposing the following indication for these products in this tentative final monograph:

"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" or "bacterial contamination") "in" (select any of the following: "minor cuts," "minor scrapes," or "minor oral irritation") (which may be followed by) "caused by" (select any of the following: "dental procedures," "dentures," "orthodontic appliances," or "accidental injury").

The Panel's Category III indication for oral antiseptics also included use of these ingredients for sore throat by decreasing the number of germs in the mouth. The agency has determined that this part of the indication should remain in Category III because inadequate data have been submitted to support a "relief of sore throat" indication.

The agency notes that the Panel discussed long-term uses of oral antiseptics to cleanse the mouth and suppress mouth odors. The agency considers such uses to be cosmetic in nature. Cosmetic claims are not subject to this rulemaking. (See section I.A., comment 3.) However, antiseptic

mouthwashes used on a long-term basis for plaque reduction are considered drugs. The agency will address the long-term use of antiseptic mouthwash products for plaque reduction in a subsequent segment of the OTC oral health care drug product rulemaking. (See section I.A., comment 1 and section I.M., comment 32.)

In conclusion, the agency agrees with the comment that a first aid claim is appropriate for OTC oral antiseptics and is proposing such a claim in this tentative final monograph. Claims related to "sore throat," "canker sores," and "denture stomatitis" are Category III because additional data are needed to support these claims for OTC oral antiseptics. The agency's evaluations of the ingredients phenol and povidone-iodine, requested by the comment for Category I classification, are discussed in section I.H., comment 14 and section I.I., comment 16. No additional data were submitted to support the efficacy of carbamide peroxide; thus, this ingredient remains in Category III in this tentative final monograph. The agency invites the submission of data to support reclassification of any oral antiseptic ingredient(s) from Category III to Category I.

References

(1) Comment No. LET004 and OTC Vols. 130132 and 130163, Docket No. 81N–0033, Dockets Management Branch.

(2) Addy, M. et al., "Trial of Astringent and Antibacterial Mouthwashes in the Management of Recurrent Aphthous Ulceration," *British Dental Journal*, 136:452–455, 1974.

(3) Olsen, I., "Denture Stomatitis—Effects of Chlorhexidine and Amphotericin B on the Mycotic Flora," *Acta Odontologica Scandinavica*, 33:41–46, 1974.

23. One comment requested that the agency amend the Oral Cavity Panel's Category III indication for oral health care antimicrobials that states "For the temporary relief of minor sore mouth and sore throat by decreasing the germs in the mouth" (47 FR 22760 at 22889). The comment claimed that a portion of the statement, "by decreasing the germs in the mouth," is not an indication for use, but is a statement of mechanism of action and should be deleted from the proposed indication. The comment stated that including a mechanism of action in the indication is not consistent with the labeling of other OTC oral health care products such as anesthetic/analgesic agents, astringents, debriding agents, or demulcents. Another comment requested that the agency place the following labeling claim in Category I for the combination of 0.045 percent cetylpyridinium chloride and 0.005 percent domiphen bromide: "Temporarily reduces bacteria in the mouth and throat."

The agency acknowledges that the Oral Cavity Panel's recommended Category III indication for oral antiseptics contains a phrase denoting a mechanism of action as does the agency's proposed Category I indication (see section I.K., comment 22). However, this type of labeling is not inconsistent with some of the labeling indications proposed by the agency for other oral health care drug products. For example, the agency's proposed indication for debriding agents, which states "aids in the removal of phlegm, mucus * * * associated with occasional sore mouth" (56 FR 48302 at 48345), and the proposed indication for demulcent drugs, which states "* * * protection of irritated areas in sore mouth and sore throat" (56 FR 48346), contain wording denoting a mechanism of action. Thus, although monograph indications do not always include a mechanism of action, at times such labeling is included in a monograph.

The agency does not believe that the labeling claim requested by one comment, "Temporarily reduces bacteria in the mouth and throat," is an appropriate indication for OTC oral health care drug products. The indication does not inform consumers of what benefit might be expected to result from reducing the bacteria in the mouth and throat. Furthermore, the agency is not aware of any data demonstrating that reducing the bacteria in the throat has a therapeutic benefit. However, the agency has no objection to labeling referring to reduction of bacteria in the mouth (e.g., temporarily reduces the number of bacteria in the mouth) appearing in the labeling of OTC oral antiseptic drug products as other information, provided it is not intermixed with labeling established by the monograph and it is not used in a false or misleading manner.

24. One comment objected to the Oral Cavity Panel's Category II classification of the indication that states "Helps provide soothing temporary relief of dryness and minor irritations of the mouth," (47 FR 22760 at 22858) for mouthwash products containing povidone-iodine. The comment mentioned that the Panel concluded that this statement indicates that the product is used for cosmetic purposes but implies that the product exerts a therapeutic effect (47 FR 22857 to 22858). The comment felt that dryness and irritation of the mouth and throat are recognized by the consumer as an abnormal condition and are thought to be synonymous with such statements as "minor irritation, pain, sore mouth, and sore throat," "discomfort," and "irritated areas in sore mouth and sore throat." The comment claimed that these statements should be permitted as an alternate or adjunct to Category I labeling for antimicrobial products, where the effects are documented with substantial evidence.

The comment added that substantial evidence was submitted to show that a povidone-iodine mouthwash provides relief of dryness and minor irritations of the mouth and throat. The comment referred to evidence supporting this indication, approved under NDA 10–290, but the comment did not include any additional data concerning this claim. The comment requested that the following indications be allowed under § 356.51 for antimicrobial drug products containing povidone-iodine: (1) "To help (or Helps) provide soothing temporary relief of dryness and minor irritations of the mouth and throat," and (2) "Aids in the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat." The comment noted that this second indication was recommended by the Oral Cavity Panel for astringent drug products.

A second comment stated that the indications "An aid to daily oral care," and "Provides soothing temporary relief of dryness and minor irritations of the mouth and throat," and any reasonably synonymous statements, should be approved for the combination of cetylpyridinium chloride 0.045 percent and domiphen bromide 0.005 percent. A third comment requested that the following claim be approved for use on products containing cetylpyridinium chloride: "For daily use as an adjunct to good oral hygiene."

In the Federal Register of December 2, 1971 (36 FR 23000), as part of the agency's DESI program, the agency stated that mouthwash and gargle products reviewed under the DESI program would now be under the purview of the OTC drug review; thus, final agency action on these products was deferred pending evaluation of the data and information concerning such products under the OTC drug review. However, in the meantime, the agency found the following labeling claims acceptable for mouthwash products, on an interim basis: "To help provide soothing temporary relief of dryness and minor irritations of the mouth and throat," "an aromatic mouth freshener," "an aid to daily care of the mouth," and "for causing the mouth to feel clean." Thus, the comments' requested indication, "To help provide soothing temporary relief of dryness and minor irritations of the mouth and throat," was allowed as a result of that DESI notice.

In this tentative final monograph, the agency is further addressing the claims permitted by that DESI notice and requested by the comments.

The agency believes that the Panel was correct in placing the statement "Helps provide soothing temporary relief of dryness and minor irritations of the mouth" and similar statements in Category II as an indication for the use of drug products containing antiseptic ingredients. However, the agency believes that the Panel erred when it included this statement under the heading of "Statements or phrases that indicate a product is used for cosmetic purposes but imply that the product exerts a therapeutic effect" (47 FR 22760 at 22857 and 22858). Statements containing phrases such as "relief of dryness" and "irritation of the mouth and throat" are more appropriate as indications for drug products containing astringents (47 FR 22904) and demulcents (47 FR 22919). Astringents alleviate irritation of the mouth and throat and demulcents exert therapeutic actions that will alleviate the conditions of "dryness" and "irritation." On the other hand, the agency does not have adequate evidence showing that antiseptic ingredients are effective in alleviating dryness or irritation of the mouth. These ingredients act by destroying microorganisms that may be present, and there is no proof that the destruction of microorganisms alleviates dryness or irritation.

Regarding the substantial evidence supporting the claim of "relief of dryness and minor irritations of the mouth and throat" mentioned by the first comment, the agency notes that no data were submitted to show that consumers associate the therapeutic activity of an antiseptic agent with the relief of dryness and minor irritations, nor were adequately controlled studies substantiating the claim included in NDA 10–290. Therefore, the agency is not proposing such claims for any antiseptic products.

The agency has already proposed a "relief of dryness" claim for demulcent ingredients as part of this rulemaking in § 356.58 of the amendment to the tentative final monograph for OTC oral health care drug products (56 FR 48302 at 48346). That claim states: "For temporary relief of minor discomfort and protection of irritated areas in sore mouth and sore throat." As mentioned by one comment, the proposed indications for oral health care astringent ingredients presently include a claim for "relief of minor irritation." (See proposed § 356.54 in the amendment to the tentative final monograph for OTC oral health care drug products (56 FR 48345).)

With regard to the other labeling claims permitted in the December 2, 1971 DESI notice and the labeling claims suggested by the second and third comments, i.e., "An aid to daily oral care" and "For daily use as an adjunct to good oral hygiene," the agency now considers these types of claims to be cosmetic claims that are not subject to this rulemaking. (See section I.A., comment 3.)

25. One comment stated that the 2-day duration of treatment recommended by the Oral Cavity Panel for antimicrobial drug products (47 FR 22760 at 22928) is insufficient "to address normal healing time." Stating that the Topical Antimicrobial Drug Products Panel provided a 7-day use limit, the comment recommended that a 7-day duration of use be adopted for this monograph.

The Oral Cavity Panel recommended the 2-day use limit for all OTC oral health care drug products because of the risk of serious illness if appropriate treatment of a sore throat is delayed. However, although a sore mouth may denote the presence of a condition that requires diagnosis and treatment by a physician, in most cases it is caused by minor ulcerations and other benign conditions that are self-limited, last only short periods of time, and generally heal spontaneously in 7 to 10 days (47 FR 22760 at 22774 to 22776). As stated in the first segment of the oral health care drug products tentative final monograph (53 FR 2436 at 2448), the agency believes that because symptoms associated with a sore mouth are unlikely to be indicative of a serious health threat, a 7-day use limitation of an OTC oral health care drug product is appropriate for the relief of symptoms of a sore mouth, e.g., pain and minor irritation. Because a sore throat can be the symptom of a serious disease and may require more immediate attention, the agency believes that it is necessary to place a 2-day limit on the use of an OTC oral health care drug product that is used to relieve symptoms of a sore throat.

For these reasons, in an amendment to the first segment of the OTC oral health care drug products tentative final rulemaking (56 FR 48302 at 48343 and 48346), the agency subsequently proposed the following warning for OTC oral health care drug products that are indicated for the relief of sore mouth and sore throat symptoms: "If sore throat is severe, persists for more than 2 days, is accompanied or followed by fever, headache, rash, swelling, nausea, or vomiting, consult a doctor promptly. If sore mouth symptoms do not improve in 7 days, or if irritation, pain, or redness persists or worsens, see your dentist or doctor promptly." For products labeled for the relief of sore mouth only, the proposed warning reads: "Do not use this product for more than 7 days unless directed by a dentist or doctor. If sore mouth symptoms do not improve in 7 days, if irritation, pain, or redness persists or worsens, or if swelling, rash, or fever develops, see your dentist or doctor promptly." (See 56 FR 48302 at 48343, 48345, and 48346.)

Likewise, the agency believes that part of this proposed warning may be applicable to OTC oral health care antiseptic drug products. At this time, sore throat claims are Category III for oral antiseptic ingredients. Therefore, in this document, the agency is not proposing the first portion of the above warning for oral health care drug products that are indicated for the relief of sore throat. If sore throat claims for oral antiseptic ingredients are upgraded to Category I, the agency will include the first portion of the above warning in the final monograph for oral antiseptic drug products. The agency is proposing in this amendment to the OTC oral health care tentative final monograph that the second portion of the above warning replace the warnings recommended by the Panel in § 356.51(c)(1)(i) and (c)(1)(ii). The agency believes that this warning fully conveys the intent of the Panel's recommended warnings. This warning is included in § 356.64(c) of this tentative final monograph in case any oral antiseptic ingredients are classified in Category I to help in reducing the chance of infection in minor oral irritations.

26. One comment requested that the agency approve the following wording, as well as reasonable variations thereof, for directions for use for OTC oral antimicrobials/antiseptics: "Rinse or gargle for 20 seconds with one ounce first thing in the morning, after meals, and before social engagements."

In this tentative final monograph, the agency is addressing only the drug use of antiseptic ingredients in oral rinses and gargles. The agency believes that the comment's suggested directions for use apply to the cosmetic use of oral antiseptic products for the suppression of oral malodor (e.g., "first thing in the morning," and "before social engagements") and for oral cleansing (e.g., "after meals"). Such directions are not appropriate for the drug use of these products and therefore are not being included in this tentative final monograph. However, antiseptic

products intended for use only as cosmetics are not subject to this rulemaking and may bear appropriate directions and other labeling for cosmetic uses. (See section I.A., comment 3.)

27. One comment requested that the following professional labeling for povidone-iodine be included in the oral health care drug products monograph: "Professional labeling—for local degerming prior to dental prophylaxis and gingivectomy." Noting that the Antimicrobial I Panel recommended labeling limited to professional use, the comment stated that professional labeling should likewise be allowed for oral health care drug products. The comment explained that the value of local degerming using povidone-iodine mouthwash in dental prophylaxis and gingivectomy procedures was shown in studies presented to the Panel (Ref. 1). The comment added that the studies demonstrated substantial evidence of the effectiveness of povidone-iodine mouthwash/gargle in significantly reducing gingival surface bacteria prior to dental prophylaxis and procedures, thereby reducing the risk of systemic infection.

In the tentative final monograph for OTC health care antiseptic drug products that will be published in a future issue of the **Federal Register**, the agency intends to propose povidone-iodine in Category I for use as a patient preoperative skin preparation, a surgical hand scrub, and a health care personnel handwash. The agency has reevaluated the data submitted to the Oral Cavity Panel (Ref. 1) and believes that some of the submitted data (Refs. 2 and 3) support the requested professional labeling for povidone-iodine in aqueous solution.

The Oral Cavity Panel stated that povidone-iodine's "application on the injection site of the oral mucosa prior to administering local anesthesia virtually eliminates all readily cultivable organisms" (47 FR 22760 at 22884). The Panel cited three studies (Refs. 2, 4, and 5) that indicate that irrigation of the gingival sulcus and rinsing the mouth with povidone-iodine immediately before tooth extraction or gingivectomy markedly reduces the incidence of associated bacteremia (i.e., the presence of bacteria in the blood). However, because two of the cited studies (Refs. 4 and 5) were published only in abstract form, the Panel considered the data insufficient in detail to be properly evaluated (47 FR 22884).

One study cited by the Panel (Ref. 2) is supportive of professional labeling for povidone-iodine solution for use in local degerming prior to dental prophylaxis and gingivectomy. In this study, 52 patients scheduled for gingivectomy were randomly divided into two equal groups. Test patients were administered a 0.5-percent povidone-iodine solution, whereas control patients were administered a placebo solution that was identical in appearance to the povidone-iodine solution but contained no povidone-iodine. Immediately prior to gingivectomy, each patient rinsed for 30 seconds with about 20 mL of the assigned preparations. The solution was then expectorated and, after a 2-minute interval, the rinsing was repeated. The sulci of the teeth in the quadrant scheduled for gingivectomy and the surrounding mucosa were then irrigated for about 1 minute using 20 mL of the assigned liquid delivered by a standard syringe with a blunt, angulated needle. Gingival surface samples were obtained by swabbing the gingiva just prior to rinsing and immediately after irrigation with the assigned preparation. These gingival swabs provided the inoculum for blood agar plates that were incubated aerobically and anaerobically at 36 °C for 48 hours. After incubation, the colonies on the plates were counted. The grading system for estimating the number of bacterial colonies per plate ranged from 1+ (i.e., few) to 4+ (i.e., too-numerous-to-count), and the major genera and/or species were enumerated. About 15 mL of blood were drawn from each patient before rinsing with the assigned preparation and within 3 minutes after the gingivectomy. The samples were cultured aerobically and anaerobically, and subsequent isolates were identified by standard bacteriological procedures.

The use of the povidone-iodine solution significantly reduced the incidence of post-gingivectomy bacteremia ($p < 0.5$). Fifteen control patients developed positive blood cultures, but only six patients in the test group developed positive blood cultures. Virtually all prerinse bacterial cultures resulted in colony count scores of 4+. Use of the test preparation produced an average decrease of 33 to 42 percent in colony count scores (for example, a decrease from a average score of 4+ to a average score of 2.7). Comparable degerming occurred for both aerobic and anaerobic bacteria.

In a double-blind clinical study (Ref. 3), Scopp and Orvieto randomly assigned 64 patients requiring dental extraction into two groups. One group of 32 patients was prepared preoperatively by gingival sulcal irrigation and rinsing with a 0.5-percent povidone-iodine oral rinse; the other 32 patients were prepared preoperatively in the same manner except that a placebo solution (colored, flavored, and packaged to match the active drug) was used for irrigation and rinsing. All patients were instructed to rinse for 30 seconds with 10 to 20 mL of the assigned oral rinse, then wait 2 minutes and repeat the rinse. The gingival sulcus of each tooth to be extracted and the surrounding gingival mucosa were then irrigated for approximately 1 minute with 10 to 20 mL of the assigned solution using a standard syringe and blunt, angulated needle. Prior to rinsing and immediately after irrigation, cultures of the gingival sulcus were obtained. Dental extraction was performed without further antisepsis. Blood samples were obtained for culture before rinsing and within 3 minutes after the dental extraction.

Bacteremia (i.e., positive blood cultures) occurred in 28 percent of the patients using the povidone-iodine oral rinse and in 56 percent of the patients using the placebo solution. The difference between the two groups is statistically significant in favor of povidone-iodine ($p < 0.05$). The gingival sulcus cultures taken immediately after rinsing and irrigation with the povidone-iodine oral rinse showed reduction or elimination of bacteria in 14 patients, no change in 17 patients, and increased growth in 1 patient. For the placebo group, the gingival sulcus cultures showed no growth and reduced growth in 1 patient each, no change in 28 patients, and increased growth in 2 patients. The difference in bacterial reduction of the gingival sac in the two groups is also statistically significant ($p < 0.01$).

The agency believes that these studies demonstrate the effectiveness of a 0.5-percent povidone-iodine aqueous solution for the preparation of the oral mucosa prior to injection, dental surgery, or tooth extraction when used by a health care professional according to the directions proposed in § 356.80(c)(3) of this tentative final monograph. However, these studies do not demonstrate the effectiveness of povidone-iodine when used by consumers as an oral antiseptic. In order for an ingredient to be classified in Category I as an oral antiseptic, the agency believes that, among other things, the ingredient should demonstrate the ability to decrease the number of bacteria in the oral cavity over an extended period of time (e.g., up to 4 hours). In addition, the ingredient should provide clinically significant benefits under OTC conditions of use (e.g., helping to prevent infection in minor wounds in the mouth, or relieving the symptoms of sore throat). (See section I.M., comment 33 for

further discussion of testing procedures.) These data demonstrate that applying povidone-iodine according to the directions proposed in § 356.80(c)(3) of this tentative final monograph results in an immediate decrease of bacteria around the operation or extraction site and a decrease of bacteremia after oral surgery or tooth extraction. Although the studies sampled the gingival mucosa surrounding the operation sites prior to and immediately after surgery or tooth extraction, they did not demonstrate a decrease in the number of oral bacteria over an extended period of time. In addition, the organisms affected by the povidone-iodine treatment were not completely identified. Furthermore, these data do not demonstrate a therapeutic benefit from the OTC use of povidone-iodine. Therefore, the agency is classifying povidone-iodine in Category III for effectiveness as an OTC oral antiseptic in this tentative final monograph. (See section I.I., comment 16.) The agency is placing povidone-iodine in Category I for use as a dental preoperative by health care professionals and is proposing labeling for such products in § 356.80.

References

(1) OTC Vol. 130176.

(2) Brenman, H. S., and E. Randall, "Local Degerming with Povidone-Iodine II. Prior to Gingivectomy," *Journal of Periodontology*, 45:870–872, 1974.

(3) Scopp, I. W., and L. D. Orvieto, "Gingival Degerming by Povidone-Iodine Irrigation: Bacteremia Reduction in Extraction Procedures," *Journal of the American Dental Association*, 83:1294–1296, 1971.

(4) Brenman, H. S., and E. Randall, "Reduction of Gingival Bacteria and Gingivectomy-Related Bacteremia by Povidone-Iodine," *International Association of Dental Research*, (Abstract #211), 1972.

(5) Randall, E., and H. S. Brenman, "Antimicrobial Action of Povidone-Iodine Mouthwash Before and During Dental Prophylaxis," *Journal of Dental Research*, 51:101, 1972.

L. Comments on Combination Oral Antiseptic Drug Products

28. One comment noted that the Dental Panel recognized that the combination of an oral antiseptic (i.e., antimicrobial agent) and an oral wound cleanser (i.e., debriding agent) was rational and should provide additional protection for an oral wound (44 FR 63270 at 63276). The Oral Cavity Panel, however, placed the same combination in Category II because it believed that the antimicrobial agent would be diluted and washed away from the diseased surface (47 FR 22760 at 22792). The comment stated that manufacturer's directions state that these products should remain in contact with the wound site for at least 1 minute. The comment added that there are active ingredients that function as antimicrobial agents as well as debriding agents and that ingredients with both properties are effective when applied locally. The comment explained that because the purpose of an antiseptic is to decrease the number of bacteria and reduce the chance of infection after minor injuries to oral cavity tissues, the combination of a debriding agent and an antiseptic provides logical therapy to reduce chances of infection, while cleansing the wound site.

In the first segment of the tentative final monograph for OTC oral health care drug products (53 FR 2436), the agency incorporated portions of the OTC oral mucosal injury rulemaking, which includes oral wound cleansers and oral wound healing agents, into the oral health care rulemaking and proposed that debriding agents and oral wound cleansers be treated as a single therapeutic class of ingredients. The agency addressed OTC oral wound healing agents separately in a final rule (51 FR 26112) and deferred consideration of the combination of an oral wound cleanser and an oral antiseptic (as recommended in § 353.20(b) by the Dental Panel) to this antiseptic segment of the rulemaking for OTC oral health care drug products.

Although the Dental Panel recommended that the combination of an oral wound cleanser and an oral antiseptic be classified as Category I, it stated in a parenthetical note that "the advisability of adding an antiseptic for the stated purpose is under review by the OTC Advisory Review Panel on Oral Cavity Drug Products" (44 FR 63270 at 63276). After reviewing both Panels' recommendations, the agency agrees with the Oral Cavity Panel's Category II classification of one or more antiseptic ingredients combined with any debriding agent. The agency is concerned that combining an antiseptic ingredient with a debriding agent/oral wound cleanser would decrease the effectiveness of the antiseptic ingredient. Because debriding agent/oral wound cleansers loosen and remove tissue, debris, mucus, etc., from mucosal surfaces by their chemical and mechanical action (e.g., foaming, lowering surface tension, and reducing viscosity of mucus), the antiseptic ingredient might not be in direct contact with the oral mucosa for a long enough period of time to exert a significant antiseptic effect, even though the manufacturer's directions state that these products should remain in contact with the wound site for at least 1 minute before spitting out. The agency believes that a reasonable time to apply a Category I antiseptic to an oral mucosal wound site or to the site of an oral inflammation is after that site has been cleansed with a debriding agent/oral wound cleanser. Additionally, the agency has surveyed the marketplace and is not aware of any currently available OTC drug product containing a combination of an oral health care antiseptic ingredient and an oral wound cleanser or debriding agent, nor were data on any such products submitted to either the Dental Panel or the Oral Cavity Panel.

The comment mentioned that some debriding agents also function effectively as antiseptic agents. However, there are no Category I debriding agent/oral wound cleansers that are also Category I antiseptic agents in this tentative final monograph.

In conclusion, for the reasons stated above, the agency is classifying the combination of an antiseptic agent and a debriding agent/oral wound cleanser in Category II in this tentative final monograph. Data are needed to show that the two ingredients are effective when used in combination.

29. Several comments pointed out that the Dental Panel had placed the following combinations in Category I in § 354.20(b), (c), and (d), respectively, of its recommended monograph: (1) An oral mucosal protectant and an oral antiseptic, (2) an oral mucosal analgesic and an oral antiseptic, and (3) an oral mucosal protectant, an oral mucosal analgesic, and an oral antiseptic. The comments noted that the Dental Panel had deferred review of the antiseptic ingredients to the Oral Cavity Panel, but that Panel failed to address locally applied antiseptics in the combinations placed in Category I by the Dental Panel. The comments maintained that these combinations are rational because the antiseptic ingredient will help to prevent or reduce possible infection while the oral mucosal analgesic will relieve the pain due to minor irritations or injury to the oral mucosa, and the addition of an oral mucosal protectant provides a coating over the wound for protection and holds the analgesic and antiseptic ingredients in place where they can act most effectively. The comments urged FDA to accept the recommendations of the Dental Panel and permit these combinations in the tentative final monograph for OTC oral health care drug products.

One of the comments added that the labeling in the tentative final monograph for OTC topical

antimicrobial drug products (47 FR 22986 at 29989) is consistent with the rationale expressed by the Dental Panel for its recommendation to place the combination of an oral mucosal analgesic and an oral antiseptic in Category I. The comment contended that the following claims could be used for topically applied oral antiseptics in such combination products:

(1) (Select one of the following: "Decreases" or "Helps reduce") "the number of bacteria on the treated area."

(2) "Helps" (select one of the following: "prevent," "guard against," or "protect against") "* * * infection."

(3) "Helps reduce the" (select one of the following "risk" or "chance") "of * * * infection."

(4) "Helps prevent bacterial contamination in minor cuts, scrapes, and burns."

The agency has reviewed the Dental Panel's discussion regarding combinations (47 FR 22712 at 22720) and, in general, agrees with that Panel that the following combinations are rational: (1) Oral antiseptic and oral anesthetic/analgesic; (2) oral antiseptic and oral mucosal protectant; (3) and oral antiseptic, oral anesthetic/analgesic, and oral mucosal protectant. In addition, the agency has reviewed the Oral Cavity Panel's evaluation of combinations containing oral antiseptic active ingredients (47 FR 22760 at 22790 to 22793) and agrees that the following combinations are reasonable: (1) Oral antiseptic and oral astringent; (2) oral antiseptic and oral demulcent; (3) oral antiseptic, oral anesthetic/analgesic, and oral astringent; and (4) oral antiseptic, oral anesthetic/analgesic, and oral demulcent. Accordingly, the agency is proposing these seven combinations in § 356.26 of this tentative final monograph.

However, this tentative final monograph does not include any Category I oral antiseptic ingredients. Therefore, these combinations will not be included in the final monograph unless at least one oral antiseptic active ingredient achieves monograph status. Further, the agency notes that the seven proposed Category I combinations may not be appropriate for all Category III oral antiseptic ingredients. For example, if hydrogen peroxide were upgraded to Category I as an oral antiseptic, it might not be appropriate to combine hydrogen peroxide with an oral mucosal protectant or an oral demulcent. As each oral antiseptic ingredient achieves monograph status, the agency will evaluate that ingredient specifically as to which combinations are suitable.

In this tentative final monograph, the indication being proposed for oral health care antiseptic drug products is similar in content to those recommended by one of the comments. (See section I.K., comment 22.) Indications for oral anesthetic/analgesic, oral astringent, oral demulcent, and oral mucosal protectant drug products were proposed in §§ 356.52(b), 356.54(b), 356.58(b), and 356.60(b) of the amendment to the tentative final monograph for OTC oral health care drug products (56 FR 48302 at 48343 to 48346).

The agency considers that the indication proposed for oral anesthetic/analgesic ingredients in § 356.52(b)(1) ("For the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat,") as not appropriate for a combination product containing an oral antiseptic because "temporary relief of sore throat" is a Category III indication for OTC oral antiseptics. (See section I.K., comment 22.) In addition, the agency considers the indication proposed for oral anesthetic/analgesic ingredients in § 356.52(b)(2) ("For the temporary relief of pain associated with canker sores") as not suitable for a combination product containing an OTC oral antiseptic ingredient because claims related to canker sores are Category III for OTC oral antiseptics. Likewise, the agency does not consider the indication proposed for oral anesthetic/analgesic ingredients in § 356.52(b)(7) for denture adhesive products containing an oral anesthetic/analgesic ("For the temporary relief of pain or discomfort of the mouth and gums due to dentures") as appropriate for products containing an oral antiseptic ingredient because there is no Category I combination that includes an oral antiseptic and a denture adhesive. Therefore, when an oral antiseptic is present in certain combination products (i.e., with: (1) An oral anesthetic/analgesic, (2) an oral anesthetic/analgesic and an oral mucosal protectant, (3) an oral anesthetic/analgesic and an oral astringent, or (4) an oral anesthetic/analgesic and an oral demulcent), the labeling of the product may not contain the indications proposed for oral anesthetic/analgesic ingredients in § 356.52(b)(1), (b)(2), and (b)(7).

Additionally, the Oral Cavity Panel recommended that oral antiseptics should not be used in children under 3 years of age (47 FR 22760 at 22928). In § 356.50(d), § 356.54(d), § 356.56(d), and § 356.58(d) of the tentative final monograph for OTC oral health care drug products, the agency proposed that the lower age limit for OTC oral health care ingredients be 2 years, except for sodium perborate monohydrate (6-year lower age limit), phenol preparations that are intended for ingestion or that could be inadvertently ingested (6-year lower age limit), tooth desensitizers (12-year lower age limit), butacaine sulfate (12-year lower age limit), and teething preparations (4-month lower age limit) (56 FR 48302 at 48343 to 48346). The agency does not believe that oral antiseptics should be used in children under 2 years of age unless done so under a doctor's supervision. Therefore, the agency is not proposing the indication for oral anesthetic/analgesic ingredients in § 356.52(b)(6) for benzocaine or phenol used in products for teething pain ("For the temporary relief of sore gums due to teething in infants and children 4 months of age and older") for a combination product containing an oral antiseptic and an oral anesthetic/analgesic or an oral antiseptic, an oral anesthetic/analgesic, and an oral mucosal protectant.

The agency does not consider the indication proposed for oral astringents in § 356.54 ("For the temporary relief of occasional minor irritation, pain, sore mouth, and sore throat") as appropriate for a combination product containing an oral antiseptic and an oral astringent because oral antiseptics are not indicated for use in relieving the discomfort of sore throat. Therefore, when an oral antiseptic is combined with an oral astringent or an oral anesthetic/analgesic and an astringent, the indication proposed for oral astringent drug products in § 356.54 is not appropriate. Instead, the agency is proposing the following indication for a combination product containing an oral antiseptic and an oral astringent: "For temporary relief of occasional minor irritation, pain, and sore mouth." The agency is also proposing that a combination product containing an oral antiseptic, an oral astringent, and an oral anesthetic/analgesic be labeled with any of the applicable indications proposed in § 356.52(b)(3), (b)(4), or (b)(5) or with the indication proposed above for a combination drug product containing an oral antiseptic and an oral astringent.

The agency does not consider the indication proposed for oral demulcents in § 356.58 ("For temporary relief of minor discomfort and protection of irritated areas in sore mouth and sore throat") as appropriate for a combination product containing an oral antiseptic and an oral demulcent because oral antiseptics are not indicated for use in relieving the discomfort of sore throat. Therefore, when an oral antiseptic is combined with an oral demulcent or an oral anesthetic/analgesic and an oral demulcent, the indication proposed for oral demulcent drug products in

§ 356.58 is not appropriate. Instead, the agency is proposing the following indication for a combination product containing an oral antiseptic and an oral demulcent: "For temporary relief of minor discomfort and protection of irritated areas in sore mouth." The agency is also proposing that a combination product containing an oral antiseptic, an oral demulcent, and an oral anesthetic/analgesic be labeled with any of the applicable indications proposed in § 356.52(b)(3), (b)(4), or (b)(5) or with the indication proposed above for a combination product containing an oral antiseptic and an oral demulcent.

The agency has determined that the indication proposed for oral mucosal protectant active ingredients in § 356.60(b)(4) ("For protecting recurring canker sores") should not be used for a combination product containing an oral antiseptic and an oral mucosal protectant because claims related to canker sores are Category III for oral antiseptics. (See section I.K., comment 22.) Therefore, when an oral antiseptic is combined with an oral mucosal protectant, the indication proposed for oral mucosal protectants in § 356.60(b)(4) is not appropriate.

The agency also notes that certain warnings proposed for oral anesthetic/analgesic ingredients in § 356.52(c)(1), (c)(5), and (c)(6), for oral astringents in § 356.54(c), and for oral demulcents in § 356.58(c)(1) would not be applicable to certain combination products containing an oral antiseptic. The warnings in § 356.52(c)(1), § 356.54(c), and § 356.58(c)(1) are partially sore throat warnings that limit use of a product to 2 days if the sore throat is severe or is accompanied by or followed by fever, headache, rash, swelling, nausea, or vomiting. These warnings are not applicable to a combination product containing an antiseptic because an oral antiseptic is not indicated for use to relieve the symptoms of sore throat. In addition, because oral antiseptics may not be used in teething products or denture adhesives, the warnings related to such products in § 356.52(c)(5) and (c)(6) are not applicable to combination drug products containing an oral antiseptic and an oral anesthetic/analgesic or an oral antiseptic, an oral anesthetic/analgesic, and any other oral health care ingredient.

Because this tentative final monograph does not include any Category I antiseptic ingredients, the agency is not proposing any directions for oral antiseptic ingredients. The agency is reserving § 356.64(d) for directions should any oral antiseptic ingredients be included in the final monograph. Likewise, for the same reason, the agency is not proposing any directions for oral health care combination drug products containing antiseptic ingredients.

Based on the above discussion, the agency is proposing to include specific indications and warnings in § 356.66(b) and (c) for the labeling of combination drug products that include an oral antiseptic. This labeling will appear in the final monograph only if at least one oral antiseptic active ingredient achieves monograph status.

30. One comment requested that the agency approve the combination of 0.045 percent cetylpyridinium chloride and 0.005 percent domiphen bromide as a Category I oral antiseptic. The comment contended that the addition of small amounts of domiphen bromide to a formulation containing cetylpyridinium chloride enhances the in vitro activity of the formulation against gram-positive and gram-negative standard bacterial cultures. The comment contended that this performance improvement satisfies even the Oral Cavity Panel's criteria for the combination of two active ingredients from the same therapeutic category having the same pharmacological mechanism of action (47 FR 22760 at 22792). The comment added that in calling for "improvement of safety or enhanced effectiveness or both," the Panel went well beyond the existing regulatory guidelines for OTC combinations in § 330.10(a)(4)(iv), which requires only that each ingredient in the combination make a contribution to the claimed effect.

The comment submitted the results of two in vitro studies designed to justify the combination of 0.045 percent cetylpyridinium chloride and 0.005 percent domiphen bromide (Ref. 1). It also submitted a published article suggesting that this combination was more effective in a clinical study than a formulation containing cetylpyridinium as the sole oral antiseptic ingredient (Ref. 2).

The agency discussed the Oral Cavity Panel's recommendations regarding combination products in the first segment of the tentative final monograph for OTC oral health care drug products (53 FR 2436 at 2450). The Panel recommended that any Category I oral health care ingredient could be combined with one or more ingredients from the same therapeutic category if each ingredient is present in its full therapeutic dose, or subtherapeutic dose where appropriate, only when there is a clear demonstration that there is an improvement of safety or enhanced effectiveness or both (47 FR 22760 at 22927). However, the agency currently uses the combination policy in § 330.10(a)(4)(iv) and its guidelines for OTC drug combination products (Ref. 3) as the criteria for evaluating all OTC combination drug products.

The combination policy in § 330.10(a)(4)(iv) states that an OTC drug may combine two or more safe and effective (Category I) ingredients when each ingredient makes a contribution to the claimed effect(s); when combining the ingredients does not decrease the safety or effectiveness of any of the individual ingredients; and when the combination, used under adequate directions for use and warnings against unsafe use, provides rational therapy for a significant proportion of the target populations. Paragraph 3 of the agency's guidelines (Ref. 3) requires that, for combinations of ingredients from the same therapeutic category with the same mechanism of action, such combinations should not ordinarily be combined unless there is some advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. The ingredients may be combined in selected circumstances to treat the same symptoms or conditions if the combination meets the OTC combination policy in all respects, 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.

Although the agency believes that the ingredients cetylpyridium chloride and domiphen bromide in the concentrations mentioned by the comment are safe for OTC use as oral antiseptics, neither ingredient has been demonstrated to be an effective oral antiseptic. (See section I.E., comment 9 and section I.G., comment 13.) The data submitted by the comment are not adequate to demonstrate the effectiveness of either ingredient or a combination of the two ingredients. The two in vitro studies tested the ingredients against only two organisms, *Staphylococcus aureus* and *Salmonella typhosa* (Ref. 1). The agency does not believe that demonstrating antiseptic effectiveness against these two microorganisms is relevant to the use of an antiseptic in the oral cavity. The published article reported the results from a study of the effects of two mouthwashes on bacterial plaque (Ref. 2). As stated in section I.M., comment 32, the agency agrees with the Panel that reduction of plaque accumulation is not an appropriate criterion for establishing oral antiseptic effectiveness. (See

section I.M., comment 33 for a discussion of appropriate testing procedures.)

References

(1) Attachment D, C00013, Docket No. 81N–0033, Dockets Management Branch.

(2) Barnes, G. P. et al., "Effects of Two Cetylpyridinium Chloride-Containing Mouthwashes on Bacterial Plaque," C00013, Docket No. 81N–0033, Dockets Management Branch.

(3) FDA, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

31. One comment stated that cetylpyridinium chloride and domiphen bromide are effective OTC oral antiseptics and that an application (NDA 14–598) for a product containing these ingredients had been approved for 18 years, i.e., up to November 17, 1982, the date of the comment. The comment stated that NDA 14–598 established the safety and effectiveness of the active ingredients, cetylpyridinium chloride 0.045 percent and domiphen bromide 0.005 percent, and their combination; and that the same combination is used today. The comment maintained that supplementation of the application and periodic reporting have supported and even strengthened the proof of safety and effectiveness. In addition, the comment stated that extensive tests demonstrating the ability of a product containing cetylpyridinium chloride and domiphen bromide to kill bacteria and viruses in vitro were reported to the Panel (Ref. 1) and are included in NDA 14–598. The comment also stated that NDA 14–598 contains the results of numerous tests showing reduction of bacterial counts after rinsing with the product and that the application contains data showing effectiveness of the product in temporarily relieving minor sore throat. The comment stated that although the bulk of the material in NDA 14–598 is not publicly available, it is in the agency's files and may be used by the agency to support these comments. Moreover, the comment contended that it regards the continuing validity of the application as conclusive evidence of the product's safety and effectiveness for use as an OTC oral antiseptic (Ref. 2).

The agency notes that data contained in an application are confidential information covered by 21 CFR 20.61 and are not publicly available. The sponsor of the application would have to affirmatively submit these data as part of the public administrative record for the agency to consider them in this rulemaking proceeding. As the agency has indicated elsewhere under similar conditions concerning an antitussive drug product containing diphenhydramine hydrochloride (48 FR 48576 at 48582), determination by FDA that a new drug is safe and effective and the approval of an application for the drug are not synonymous with a determination that a drug is generally recognized as safe and effective in the OTC drug review. See *Weinberger* v. *Bentex Pharmaceuticals, Inc.*, 412 U.S. 645, 651 (1973). In addition, the agency is aware that the commentor requested that approval of NDA 14–598 be withdrawn because the product was no longer being marketed as a drug (Ref. 4).

General recognition of the effectiveness of a drug in the OTC drug review must be based on adequate published or publicly available medical and scientific data. (*United States* v. *41 Cases * * * Naremco*, 420 F.2d 1126 (C.A. 5, 1970); *United States* v. *An Article of Drug * * * Mykocert*, 345 F. Supp. 571 (D.C. 1972); *United States* v. *An Article of Drug * * * Asper Sleep, CCH F.D. and Cosm. L. Rep.* 40,821 Civil No. 70–C–196 (N.D. Ill. 1971); *United States* v. *An Article of Drug * * * (Furestorol Vaginal Suppositories* 294 F. Supp 1307 (N.D. Ga. 1968).) There is not adequate information publicly available at this time to demonstrate that cetylpyridinium chloride, domiphen bromide, or the combination of the two ingredients are generally recognized as effective for the Category I indication proposed in this document. Therefore, the agency is unable to conclude at this time that these ingredients or a combination of these ingredients are generally recognized as effective oral antiseptic agents, and is proposing that they be Category III for effectiveness. (See section I.E., comment 9; section I.G., comment 13; and section I.L., comment 30.)

References

(1) OTC Vols. 130078, 130118, 130134, 130160, and 130187.

(2) Attachment F, Comment No. C00013, Docket No. 81N–0033, Dockets Management Branch.

(3) Attachment G, Comment No. C00013, Docket No. 81N–0033, Dockets Management Branch.

(4) Letter from W. E. Cooley, The Procter & Gamble Co., to the Division of Radiopharmaceutical, Surgical, and Dental Drug Products, FDA, NDA 14–596, dated January 5, 1990, OTC Vol. 130CTFM.

M. Comments on Testing

32. Addressing the Oral Cavity Panel's consideration of protocols for testing antiseptic mouthwashes, two comments stated that the measurement of plaque reduction is a valid technique to assess the antimicrobial activity of oral antiseptics. Noting that dental plaque is largely composed of living bacteria within a polysaccharide matrix, one comment contended that experts recognize that "antiseptic activity may be measured in the mouth by taking counts of unattached organisms before and after treatment, or by measuring plaque differences among subjects receiving either the test substance or a control." The comment mentioned that the Panel's minority report outlines a scheme of reasonable in vitro and in vivo tests that are well accepted and have been shown to be satisfactory in demonstrating the antiseptic activity of mouthwashes (47 FR 22760 at 22893 to 22901). The comment added that, in 1978, the Oral Cavity Panel voted approval of the clinical protocols needed to support Category I status for oral antimicrobials for use in mouthwashes, and that a professional association of manufacturers concurred with that recommendation. The comment urged that these protocols be reinstated as the proof required to obtain Category I status for antimicrobial mouthwashes.

Also citing the Panel's minority report, the second comment stated that the majority of the Panel, at its next-to-last meeting, voted to reject the testing guidelines for demonstrating antiseptic activity that the Panel had recommended to industry over the course of several years and that the firm submitting the comment had relied upon to confirm its product's antiseptic properties. Although pointing out that the majority of the Panel evidently desired an objective test to justify plaque reduction as a criterion for establishing antimicrobial activity (47 FR 22760 at 22841), the comment contended that such an objective test was originally prescribed by the Panel and successfully conducted for the firm's mouthwash product containing a combination of volatile oils. The comment stated that reductions in dental plaque biomass have been shown to correlate with reductions in dental plaque bacteria by objective weight measurement (47 FR 22894 to 22895) and that other equally valid plaque reduction measurements, such as area measurement, were also successfully conducted for the firm's product. The comment concluded that these "state of the art" plaque reduction measurements should be accepted as indices of antiseptic action.

The agency is aware that the majority of the Panel stated that "the rationality of plaque reduction as a criterion of effectiveness of antimicrobial agents for use in the mouth and throat is highly debatable, and evidence of the validity of the method is scant. Plaque

reduction, therefore, is not accepted by this Panel as a criterion for determining effectiveness of antimicrobial agents for oral health care products intended to treat sore mouth or sore throat," (47 FR 22840). The agency agrees with the Panel and believes that plaque reduction has not been established as a valid technique for determining the antiseptic effectiveness of ingredients used for the types of indications being considered in this segment of the tentative final monograph: (1) First aid to help prevent infection in the mouth, or (2) for the temporary relief of minor sore throat symptoms.

The agency believes that the types of tests suggested in the Panel's testing guidelines at 47 FR 22760 at 22890 to 22893 are better suited to demonstrate the effectiveness of antiseptic ingredients in reducing the risk of infection in the oral cavity or in relieving sore mouth and sore throat symptoms. These testing guidelines are further discussed in section I.M., comment 33. However, as discussed in the previous segments of this tentative final monograph (see 53 FR 2436 and 56 FR 48302), in developing this monograph the agency is not addressing specific testing guidelines for upgrading ingredients to Category I. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. The revised procedures also state the time in which test data must be submitted for consideration in developing the final monograph. (See also part II. paragraph A.2.—*Testing of Category II and Category III conditions.*)

The agency wishes to point out that, as discussed in the call-for-data for antiplaque ingredients and claims (55 FR 38560), the Dental Products Panel will evaluate data regarding the safety and effectiveness of active ingredients contained in products displaying antiplaque and antiplaque-related claims. A subsequent segment of the rulemaking for OTC oral health care drug products will cover that Panel's recommendations to the agency regarding drug ingredients used for the reduction of plaque and plaque-related claims. Methods discussed by the comments and by the minority of the Oral Cavity Panel may be appropriate to demonstrate antiseptic activity of ingredients intended to reduce or prevent plaque.

33. Two comments stated that presentations had been made to the Oral Cavity Panel concerning guidelines for in vitro and in vivo testing of topical antiseptics (Refs. 1, 2, and 3) and that these data were not considered or included in that Panel's discussion. The comments contended that the guidelines were adequate to test ingredients for effectiveness and to establish a first aid antiseptic category for oral health care drug products that meet these guidelines. The comments stated that the guidelines provide for a statistically significant reduction in vivo combined with a 95-percent reduction in vitro of the organisms tested and, thus, provide proof of clinically useful antiseptic activity.

One comment paraphrased an agency statement that was published in the tentative final monograph for OTC topical antimicrobial drug products (i.e., first aid antibiotic drug products) (47 FR 29986 at 29991 to 29992) as follows:

> The agency agrees with the comments that minor skin injuries, such as cuts and scrapes, are self-healing and that the body's healing mechanisms can handle some infections that might develop in these injuries. However, as the reply comment pointed out, some minor skin injuries do not heal without treatment and it is impossible to make that distinction at the time of injury. It is well documented that applying topical antibiotics to skin wound lesions reduces the number of bacteria at the site of application and serves as an adjunct to cleansing wounds.

The comment argued that, in view of the agency's medical assessments of topical antibiotics as stated above, clinical testing of each ingredient or product is unnecessary. The comment felt that in vitro data demonstrating that a product's active ingredient is effective against the organism(s) likely to be found at the site should be sufficient to allow classification in Category I. The comment added that such a decision would be consistent with the agency's acceptance of all Category I topical antibiotics for the first aid indication to help prevent infection in minor cuts, scrapes, and burns (47 FR 29986 at 29999).

The Oral Cavity Panel considered the presentations concerning guidelines for in vitro and in vivo testing (Refs. 1, 2, and 3) and made suggestions concerning requirements for conducting such studies designed to obtain data for reclassifying Category III ingredients to Category I for safety and effectiveness or both (47 FR 22760 at 22890 to 22893). The Panel suggested that preliminary, well-designed in vitro studies be required to demonstrate antiseptic effectiveness and that the data obtained from in vitro studies be verified and supported by in vivo animal and human studies. The Panel stated that human model studies should be followed by appropriate clinical trials. The Panel included recommendations for in vitro and in vivo testing procedures to indicate the types of data necessary to upgrade ingredients from Category III to Category I and provided suggestions for obtaining such data.

Clinical Testing of OTC Oral Antiseptics

The agency believes that data from in vitro testing alone are insufficient to establish that an oral antiseptic is generally recognized as effective in: (1) Decreasing the number of microorganisms in the oral cavity and thus helping to prevent or reduce the chance of infection or bacterial contamination in minor oral wounds, or (2) temporarily relieving the symptoms of minor sore throat or mouth. The agency's assessment of the effectiveness of topical antibiotics in helping to prevent infection in minor skin cuts, scrapes, and burns (47 FR 29986 at 29991 to 29992) is not relevant in evaluating the effectiveness of oral antiseptic ingredients in helping to prevent infection in minor wounds in the mouth. Although demonstrated in vitro antiseptic bactericidal or bacteriostatic action is of predictive value in projecting clinical efficacy for antiseptics used on the skin (39 FR 33103 at 33110 and 56 FR 33644 at 33671), the agency believes that such activity alone is not sufficient to allow classification of an ingredient in Category I.

The environment of the oral cavity is very different from that of the skin. The oral cavity supports one of the most concentrated and varied microbial population of the body. The total microscopic count of saliva has been given as anything from 43 million to 5.5 billion per mL with an average of about 750 million. The microbial concentration of the gingival sulcus and in plaque is at least 100 fold greater, or approximately 200 billion cells per gram of sample (Ref. 4). Conversely, the skin, for the most part, is an inhospitable place for most microorganisms because the secretions of the skin are acidic and most of the skin contains little moisture (Ref. 5). The agency believes that, on the fairly dry surface of the skin, a reduction in microorganisms caused by the application of a topical antiseptic will persist for some time and, thus, may help to prevent minor skin infections. However, even if one could demonstrate a reduction of microorganisms on a site in the oral cavity, it is unlikely that this reduction

would result in a therapeutic benefit because the action of saliva would reinoculate the site almost immediately. As the Oral Cavity Panel stated, approximately 0.25 to 1 mL of saliva is excreted per minute in the oral cavity (47 FR 22766). Therefore, oral surfaces are constantly bathed with saliva, and organisms are readily transported from one area of the mouth to another. This may be particularly true of minor oral irritations, cuts, and scraps where there is an almost irresistible urge to probe the site with the tongue. This continuous reinoculation of the site with large numbers of microorganisms is likely to counteract any therapeutic benefit that might result from topical antiseptic action in the oral cavity. Therefore, the agency tentatively concludes that clinical testing is necessary to demonstrate that an antiseptic ingredient truly has a therapeutic effect in the oral cavity.

Clinical trials to demonstrate the effectiveness of an OTC oral antiseptic ingredient should be well-designed and well-controlled. Such trials should be structured to closely approximate the clinical situations for which a product is intended to be used and to substantiate proposed claims. These studies should demonstrate that the topically-applied antiseptic ingredient helps to prevent infection in minor wounds in the mouth better than the vehicle alone.

In Vivo Testing Procedures

Three in vivo studies submitted to the Panel (Ref. 2), and mentioned by the comments, were designed to answer specific questions raised by the Panel during its evaluation of in vivo testing guidelines for oral antiseptics (Ref. 1). The basic method used in the three studies (Ref. 2) involved the use of 10 normal subjects with no medical problems. The subjects were treated with cetylpyridinium chloride (0.1 or 1 percent) and a placebo (distilled or deionized water). In some of the studies, a template was used to define the cheek treatment area, and in other studies, no template was used. Each subject served as his or her own control. The technique consisted of using a swab to sample the cheek before treatment, treating the cheek with the designated agent (i.e., active ingredient or placebo), and sampling again 1 minute later. Samples were mixed, serially diluted, plated, incubated, and visible bacterial colonies counted. A variety of mixing, plating methods, and environmental conditions were used (e.g., drop plate counting method, standard plating procedures, sonication, and incubation under carbon dioxide, aerobic, and anaerobic conditions.) The results of all three studies indicated that cetylpyridinium chloride decreased the number of bacteria within 1 minute after application on the cheek. Individual studies included the following results: (1) Subjects differ from each other by 10 to 100 fold in their normal bacterial counts, but vary little from 1 day to another in their own bacterial counts; (2) a swab sampling procedure and a drop-plate counting method are sensitive, adequate methods to detect small decreases in bacterial counts in a 10-subject panel, and decreases smaller than 2 logs or 100 fold are significant; (3) a template is not necessary to limit the treatment area; (4) successive samples taken before treatment invariably decrease, as do samples taken after treatment with water while samples taken after treatment with cetylpyridinium chloride level off or increase in successive samples, indicating that the antiseptic killed bacteria in the top layer of the oral mucosa but not in the lower layers; (5) sonication of swab samples increases the sensitivity of the method, but does not affect the estimate of antiseptic effectiveness; thus, this method may be used optionally; (6) conventional plating methods and other well-tested plating methods are highly reproducible; and (7) although results for all three incubation environments were essentially the same, the effect of some oral antiseptics could have differing effects against types of bacteria requiring specific gaseous environments; thus, three environments should be used in future studies.

The agency concludes that the techniques of the in vivo testing guidelines presented to the Panel for demonstrating the effectiveness of a locally applied antiseptic ingredient (Refs. 1 and 2) represent a partial guide for helping to assess an ingredient's effectiveness as an OTC oral health care antiseptic, but are not totally adequate for that purpose. The agency believes that in vivo testing methods used to help demonstrate the effectiveness of oral health care antiseptic ingredients should stipulate the specific organisms to be tested, the acceptable decrease in bacterial numbers, and the period of time for which the antiseptic activity should persist. The Panel's discussion of in vivo testing did not include such information (47 FR 22760 at 22891). Such testing methods should also take into account the following: (1) The normal flora of the site to be used in the study, (2) the complexity of the oral flora, (3) the site-to-site variation of the oral flora within the mouth, (4) when tissue is abraded, burned, or punctured, sites may be exposed that allow the binding of oral microorganisms that would not otherwise reside in that particular ecological niche, and (5) what shifts in the balance of the flora and/or colonization by other species are to be expected if the site is abraded or otherwise damaged. A spectrum of activity against a representative battery of organisms should be developed (i.e., *Candida albicans*, representative actinomyces and streptococcal species, and other flora frequently isolated from the site). A thorough review of the literature should identify the appropriate microorganisms.

In addition, the in vivo testing guidelines presented to the Panel (Ref. 1) did not include adequate sampling intervals after treatment with the oral antiseptic. Using the guidelines, a statistically significant difference was obtained between treatment of the cheek with the placebo and treatment with cetylpyridinium chloride; however, the length of time that the antiseptic effect persists past the 1-minute time interval used in the studies was not explored. The transient decrease in the number of bacteria at the 1-minute interval after cetylpyridinium chloride application, as noted in the comment's studies (Ref. 2), is not unexpected. The ability to maintain such a decrease over a reasonable interval of time is more significant and important, especially when one considers the effect of the oral environment. The agency believes that, for demonstrating antiseptic activity in the oral cavity, more appropriate time intervals might be 1 minute, 10 minutes, 30 minutes, 1 hour, 2 hours, and 4 hours.

The agency also believes that it might be useful to use more than one incubation environment because some microniches in the oral cavity (e.g., the gingival crevice) support anaerobic growth, and organisms commonly isolated from the oral cavity include facultative anaerobes as well as strict anaerobes. One approach would be to use a nonselective medium under anaerobic and carbon dioxide conditions and several selective media under appropriate conditions depending upon the microorganism of interest.

In Vitro Testing Procedures

The agency believes that the Panel's proposed in vitro testing guidelines represent a good starting point for the design of in vitro studies to help upgrade a Category II or Category III oral antiseptic ingredient to Category I (47 FR 22760 at 22890 to 22891. However, all such testing should be designed

using the most current technology available.

Although the agency offers the above comments on clinical, in vivo, and in vitro testing as guidance, specific testing guidelines for upgrading ingredients to Category I are not included in this monograph. (See part II. paragraph A.2.—*Testing of Category II and Category III conditions.*) Instead, the agency will meet with industry representatives or other interested parties at their request to discuss testing protocols. Any party interested in conducting studies should request a meeting at its earliest convenience. (See also section I.M., comments 32 and 35.)

The above discussion applies only to the testing required to upgrade OTC oral antiseptic ingredients from Categories II or III to Category I. In addition, the agency has tentatively concluded that final formulation testing of OTC oral antiseptic drug products is necessary. For a further discussion of such testing, see part II. paragraph B.10—Summary of the Agency's Changes.

References

(1) OTC Vol. 130117, Docket No. 81N–0033, Dockets Management Branch.

(2) OTC Vol. 130132, Docket No. 81N–0033, Dockets Management Branch.

(3) OTC Vol. 130163, Docket No. 81N–0033, Dockets Management Branch.

(4) Burnett, G. W., H. W. Scherp, and G. S. Schuster, "Oral Microbiology and Infectious Disease," The Williams and Wilkins Co., Baltimore, 1976, p. 219.

(5) Tortora, G. J., B. R. Funke, and C. L. Case, "Microbiology, An Introduction," The Benjamin Cummings Publishing Co., Inc., Redwood City, CA, 1989, p. 502.

34. Three comments disagreed with the Oral Cavity Panel's discussion concerning chlorhexidene as a standard for testing the effectiveness of oral antimicrobials. One comment stated that the use of chlorhexidene is inappropriate and unnecessary for this class of products and that the proposed guidelines for topically applied antiseptics for use on the skin do not include chlorhexidene as a standard. The second comment stated that the use of chlorhexidene as a standard is unreasonable because its usefulness is currently at issue, and the drug is not yet accepted as a safe and effective oral antiseptic. The third comment stated that chlorhexidine is unproven as a standard reference for pathogens responsible for the production of sore throat and sore mouth.

The agency acknowledges that neither the tentative final monograph for OTC antimicrobial drug products (43 FR 1210) nor the amended tentative final monograph (now called OTC first aid antiseptic drug products) (56 FR 33644) includes chlorhexidene as a standard for topical antiseptics. However, since the comment was submitted, a chlorhexidene antiseptic mouthwash has been approved for oral use in the U.S. (Ref. 1).

The Oral Cavity Panel's minority report recommended an in vitro test utilizing chlorhexidene as a standard and recommended that all antimicrobial oral products be compared to the standard (47 FR 22760 at 22897). However, as discussed in section I.M., comment 32, the testing procedures recommended by the minority of the Panel are not being accepted by the agency for testing the active ingredients that are included in this segment of the oral health care drug products rulemaking.

In its in vitro testing procedure for determining the effectiveness of oral antimicrobials, the majority of the Panel recommended the use of a positive standard control to validate the test procedure by assuring the consistent susceptibility of the test organisms. The Panel's majority report stated that "chlorhexidene digluconate, 0.2 percent in sterile water, is acceptable for this purpose," (47 FR 22891). The agency does not agree with the Panel that chlorhexidine is an appropriate positive control for this purpose. Determining whether or not an organism is susceptible to chlorhexidine does not correlate to whether or not the organism is susceptible to the test ingredient. Furthermore, as discussed in prt II. paragraph B.10—Summary of the Agency's Changes, the agency is suggesting that the active ingredient, in a suitable inactive medium, be used as a positive control.

Reference

(1) "Physician's Desk Reference," 47th ed., Medical Economics Data, Montvale, NJ, 1993, pp. 1867–1868.

35. Two comments stated that the Oral Cavity Panel's guidelines for testing topically applied antimicrobials (47 FR 22760 at 22890 to 22893) should permit variations in the methods used. One comment mentioned that variations should be allowed depending on the ingredient being tested. As an example of an appropriate variation, the other comment suggested that a method that had been submitted to the Panel would provide adequate status of in vivo antimicrobial activity (Ref. 1). The comment described that method as "swabbing of the active ingredient three times using a template and comparing this to a control."

The agency is not including specific guidelines for upgrading active ingredients to Category I in this document. Instead, the agency will meet with industry representatives at their request to discuss testing protocols and, therefore, revisions may be made from time-to-time. (See section I.E., comment 8; section I.G., comment 12; and section I.M., comment 33 for a discussion of appropriate testing procedures.)

The agency notes that the procedure referred to by one comment calls for volunteer subjects with no symptoms of an oral disease state. The agency does not believe this procedure by itself will provide adequate proof of the in vivo effectiveness of an oral antiseptic.

Reference

(1) OTC Vol. 130153.

36. Referring to the Oral Cavity Panel's discussion of in vivo testing, two comments disagreed with the suggested protocol for the determination of an antimicrobial ingredient's adverse effect on wound healing (47 FR 22760 at 22892). The comment felt that the procedure described by the Panel would be impossible to control if there were only one wound in the mouth. Expressing the opinion that, in order to compare the rate of healing, a controlled study would require multiple wounds, of comparable size and depth, in comparable locations in the mouth, and at a comparable stage in the healing process, both comments considered it virtually impossible to find such a situation occurring naturally in human subjects. The comments agreed with the Panel that such a study could be done in animals, but felt that animal studies would be of little value because animals have different microbial populations than humans. One of the comments added that if a product does not have an excessively high degree of substantivity, the risks of retarding wound healing are limited and such tests are unwarranted.

The agency agrees with the comments that it would be almost impossible to find a representative population of human subjects with multiple mouth wounds so that one wound could serve as a test site and another as a control site in the same subject. However, the agency believes that the Panel was referring to a "controlled study" as one in which a population of subjects with comparable wounds is divided into a group that is treated with the test ingredient and a group that receives a control, such as the vehicle lacking the test ingredient. In the Panel's discussion of general considerations applying to the testing for recategorization of Category III oral health care ingredients (47 FR 22760 at 22782 to 22783), the design for a controlled study is described as one in which subjects who have similar conditions are divided into

a treated group and a placebo group. In the discussion cited by the comments (47 FR 22891), the Panel stated that control groups should receive treatment with inert vehicles that are identical in appearance, color, and consistency to the test materials. The agency believes that the general principles stated above can be coordinated so that well-controlled studies to investigate the adverse effects of oral health care antimicrobial ingredients on wound healing could be designed according to the Panel's recommendations.

The agency disagrees with the comments' belief that animal studies are of little value and concurs with the Panel's position on animal studies. Although believing that the final appraisal of an oral antiseptic must be done by clinical trials, the Panel recommended that in vivo testing, including animal and human models, should be performed prior to clinical studies (47 FR 22891). The agency agrees that an initial assessment of safety and effectiveness of a drug should be made using animal models before the test formulation is given to humans in a controlled clinical study.

However, the agency does not believe that further wound healing studies are necessary for OTC oral antiseptic ingredients. As part of the rulemaking for OTC topical antiseptic drug products, the agency has reviewed many studies designed to show the effect of antiseptic ingredients on wound healing. The agency's conclusions on these data are stated in the tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33658, 33660, and 33662). Several of the first aid antiseptic ingredients for which wound healing studies were submitted are also classified as Category III oral antiseptic ingredients, i.e., benzalkonium chloride, iodine, and povidone-iodine. The submitted studies show that these antiseptic ingredients do not delay wound healing when used for a short period of time, i.e., 7 days, on limited areas of the body. The agency believes that these wound healing data are also relevant to oral antiseptic ingredients that are limited to a maximum of 7 days of use on the affected area of the mouth and throat. The Panel was concerned about the lack of data on possible adverse effects on the oral mucosa resulting from the use of oral antiseptic drug products on a daily basis for months at a time (47 FR 22760 at 22834). However, the agency is proposing labeling limiting self-medication with these products to a 7-day period for relief of the symptoms of sore mouth. (See section I.K., comment 25.) In addition, the oral antiseptic ingredients are used in lower concentrations than the first aid antiseptic ingredients and are in contact with the affected area for a shorter time period following application. This occurs because the oral antiseptic ingredients are mixed with the saliva of the mouth and then expectorated. Therefore, oral antiseptic ingredients would not be expected to delay wound healing. For the above reasons, the agency concludes that additional studies to demonstrate that oral antiseptic ingredients do not delay wound healing are unnecessary. Further, according to 21 CFR 310.534(b), any OTC drug product that is labeled, represented, or promoted for use as an oral wound healing agent (e.g., "promotes wound healing") is regarded as a new drug, and an approved application is required before marketing.

37. One comment stated that the Oral Cavity Panel's recommended studies to prove that antiseptic mouthwashes aid in the treatment of sore mouth and sore throat are not feasible for the following reasons: (1) It is not feasible to attempt to collect enough data in any reasonable period of time from volunteers who have symptoms of a sore throat or sore mouth due to the unique infection with a single pathogen in order to prove specific activity of an antibacterial agent (47 FR 22760 at 22779); (2) Koch's Postulates would be virtually impossible to fulfill because proof of the presence of the offending etiologic agent specifically responsible for the sore mouth/sore throat, in addition to correlation of relief of symptoms of sore mouth/sore throat with a decrease or elimination of the etiologic agent, could of itself be impossible to achieve; (3) complementary animal studies simulating these symptoms would be difficult to perform without the introduction of a systemic pathogen and, under these circumstances, the natural conditions specified as a prerequisite for proof of efficacy could not be approximated (47 FR 22890); (4) the test organisms originally approved by the Panel to demonstrate antimicrobial activity (the Bahn test), *Streptococcus mutans, Actinomyces viscosus, C. albicans* and optionally, *Pseudomonas aeruginosa*, have no precedent for use as test organisms for antibacterial activity relating to production of symptoms of sore mouth or sore throat; and (5) such studies must by necessity avoid the use of any systemic antimicrobial agent and would obviously create a situation which is not only medically unsound but also unethical.

In its discussion of the data required for the evaluation of oral antiseptic ingredients (47 FR 22760 at 22890 to 22893), the Oral Cavity Panel recommended general principles applicable to the design of experimental protocols for demonstrating the safety and efficacy of these ingredients. The Panel did not consider its recommendations for testing the effectiveness of these ingredients to be mandatory requirements, but presented its recommendations merely to indicate the types of data it considered necessary and to provide suggestions for obtaining such data. The agency is adopting this approach and treating the Panel's recommendations as guidelines for obtaining data to upgrade Category II or Category III ingredients to Category I. However, in this tentative final monograph, the agency is proposing testing procedures for final formulations containing Category I oral antiseptics. (See section I.M., comments 32 and 35.)

The Panel recognized that it would be impossible to propose a single general protocol because of the diverse etiology of oral inflammation. The Panel recommended that the data obtained in support of Category I status for oral antiseptic ingredients show that preparations applied to the mucous membranes of the mouth and throat act topically and relieve symptoms caused by an infection by reducing pathogenic microbial populations (47 FR 22760 at 22890), but it also recognized that appropriate individual tests must be devised to demonstrate this for a particular ingredient and that the responsibility of selecting or devising reliable methods for procuring acceptable evidence of the effectiveness of an ingredient rests with the manufacturer sponsoring the product.

The agency is, however, proposing testing procedures for OTC oral antiseptic final formulations in § 356.90 of this tentative final monograph. In those testing procedures, the agency is accepting the Panel's recommendations regarding the use of *S. mutans, A. viscosus*, and *C. albicans* as test organisms. (See Part II. paragraph B.10—Summary of the Agency's Changes.) These organisms are representative of organisms commonly found in the oral cavity. The agency believes that a decrease in the number of these organisms in the proposed in vitro testing procedures indicates that the final formulation of a product has not decreased the effectiveness of a Category I oral antiseptic.

II. The Agency's Tentative Conclusions and Adoption of the Panel's Report

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

1. *Summary of Ingredient Categories.*

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

Antiseptic Active Ingredients	Panel	Agency
Alcohol	III	III
Benzalkonium chloride	III	III
Benzethonium chloride	III	III
Benzoic acid	III	III
Boric acid	II	II
Boroglycerin	II	II
Camphor	II	II
Carbamide peroxide in anhydrous glycerin	III	III
Cetalkonium chloride	III	III
Cetylpyridinium chloride	III	III
Chlorophyllin copper complex	III	III
Cresol	II	II
Dequalinium chloride	III	III
Domiphen bromide	III	III
Eucalyptol	III	III
Ferric chloride	II	II
Gentian violet	III	II
Hydrogen peroxide	III	III
Iodine	III	III
Menthol	III	III
Meralein sodium	II	II
Methyl salicylate	III	III
Nitromerso	III	II
Oxyquinoline	III	III
Phenol preparations (phenol and/or phenolate sodium)	III	III
Potassium chlorate	II	II
Povidone-iodine	III	III
Secondary amyltricresols	III	III
Sodium caprylate	III	III
Sodium dichromate	II	II
Thymol preparations (thymol and thymol iodide)	III	III
Tincture of myrrh	II	II
Tolu balsam	III	III

2. *Testing of Category II and Category III Conditions.*

The Oral Cavity Panel recommended testing guidelines for OTC oral health care antimicrobial drug products (47 FR 22760 at 22890 to 22893). The agency's position regarding these testing guidelines is discussed in Part I, paragraph E of this document. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any OTC oral antiseptic active 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

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

1. In order to be consistent with terminology used in the rulemaking for OTC topical antiseptic drug products, the agency is proposing to replace the Panel's term "antimicrobial" with the term "antiseptic" in this tentative final monograph. (See section I.A., comment 1.)

2. The agency is not including in this tentative final monograph the Panel's definition for an antimicrobial agent in § 356.3(c) of its recommended monograph (47 FR 22760 at 22927). Instead, the agency is proposing to add definitions for the terms "antiseptic drug" and "oral antiseptic" to § 356.3 of this tentative final monograph. (See section I.K., comment 20.)

3. The Oral Cavity Panel concluded that gentian violet was safe for use in the oral cavity, but that there were insufficient data available to permit final classification of its effectiveness as an oral antiseptic (47 FR 22760 at 22873 to 22875). The Panel based its safety determination on several factors: (1) the oral LD_{50} of gentian violet in mice and rats is 1.2 to 10 g/kg; (2) it is nontoxic when applied to the mucous membrane and skin; and (3) gentian violet has been used orally in both children and adults as an anthelmintic. However, the Panel noted that when gentian violet is ingested, it may cause nausea, vomiting, diarrhea, and lassitude, and that intravenous injection of impure preparations may produce a severe shock-like reaction.

Regarding the use of gentian violet as an anthelmintic, in its report on OTC anthelmintic drug products published in the **Federal Register** of September 9, 1980 (45 FR 59540), the Miscellaneous Internal Panel reviewed the information available to it regarding the safety of gentian violet and acknowledged both a scarcity of acute toxicity data and "a high incidence of undesirable side effects associated with its clinical use in children." That Panel also reviewed reports regarding the potential carcinogenicity of gentian violet and recommended "that further testing be performed to resolve the carcinogenic concerns." According to the Miscellaneous Internal Panel, these concerns were not convincing when weighed against the lack of adverse effects reported during the long marketing history of gentian violet. Thus, that Panel concluded that gentian violet was safe when used as directed. FDA, however, reviewed the available data relevant to the genetic toxicity of gentian violet and stated in its preamble to the Panel's report on OTC anthelmintic drug products that a definitive conclusion regarding the carcinogenic activity of gentian violet could not be reached at that time. On the basis of the available evidence, the agency nominated gentian violet for study in the NTP. The agency concluded that the potential risk of using gentian violet as an oral anthelmintic outweighed the benefits and announced its intent to classify gentian violet in Category II in the tentative final monograph for OTC anthelmintic drug products (45 FR 49540).

In that tentative final monograph published in the **Federal Register** of August 24, 1982 (47 FR 37062 at 37063), the agency further discussed the genetic toxicity of gentian violet, and reaffirmed its earlier conclusions regarding the safety of gentian violet. In that proposal, gentian violet was classified in Category II as an oral anthelmintic. In the final rule published in the **Federal Register** of August 1, 1986 (51 FR 27756 at 27758), the agency determined that gentian violet is a nonmonograph drug for OTC anthelmintic use.

In a proposed rule published in the **Federal Register** of February 13, 1990 (55 FR 5194) regarding the safety of gentian violet in animal feed, FDA discussed the National Center for Toxicology Research's (NCTR) series of studies that provide additional new information on the toxicity and carcinogenicity of gentian violet. One lifetime study (chronic study) showed

gentian violet to be a carcinogen in mice. Another lifetime study in rats also resulted in a carcinogenic response. A residue study showed that residues of gentian violet occurred in the edible tissues of chickens after they were administered gentian violet. Reproductive-teratology studies were negative or inconclusive. A multigeneration study in rats showed a lower body weight, a dose-related necrosis in the thymus, and a dose-related effect on the kidneys in females. However, a pairwise statistical evaluation of these parameters was not performed. Metabolism studies in rats and mice showed that orally administered gentian violet is absorbed, with the highest residue levels of the compound and its metabolites occurring in fat and liver. The proposal also discussed the results of an extensive search of the published literature relevant to the safety of gentian violet (55 FR 5194 at 5200).

The agency concluded that even if the chronic studies that had been performed by NCTR did not establish that gentian violet is an animal carcinogen, they did not establish that gentian violet is safe. There is a paucity in the scientific literature of the kind of studies that are needed to support an expert opinion that gentian violet is generally recognized as safe. In fact, FDA's literature survey generally found that gentian violet tends to have mutagenic, genotoxic, and other toxic properties. FDA believes where such incriminating studies exist, experts generally agree that chronic studies must affirmatively show that the substance does not cause cancer before it can be recognized as safe (55 FR 5194 at 5201). The agency concluded that gentian violet is not generally recognized as safe for use in animal feed or as a food additive. The agency also concluded that gentian violet for veterinary drug use in food animals is not generally recognized as safe and effective and is a new animal drug (55 FR 5201).

In the **Federal Register** of August 15, 1991 (56 FR 40502), the agency issued a final rule amending its regulations (21 CFR 500.29) to declare that gentian violet is neither generally recognized as safe nor prior sanctioned and is a food additive when added to animal feed for any nondrug use. The agency also amended its regulations (21 CFR 500.30) to reflect its determination that gentian violet is not generally recognized as safe, not generally recognized as effective, or not "grandfathered" under the Drug Amendments of 1962 (Pub. L. 87–781). Therefore, gentian violet is a new animal drug when used for any veterinary drug purpose in food animals.

Based on the above, the agency concludes that gentian violet is not safe for use as an oral antiseptic. Therefore, in this tentative final monograph, the agency is reclassifying gentian violet from Category III to Category II.

4. The agency believes that the safety data evaluated by the Panel are sufficient to conclude that cetylpyridinium chloride, domiphen bromide, and povidone-iodine are safe for use as OTC oral antiseptics when labeled for short-term use (not to exceed 7 days). However, there are insufficient data to demonstrate the effectiveness of these ingredients, and they are classified in Category III. (See section I.E., comments 8 and 9; section I.G., comments 12 and 13; and section I.I., comments 15 and 16.)

5. The agency is proposing the following combinations in § 356.26 (and labeling for these combinations in § 356.66): (1) oral antiseptic and oral anesthetic/analgesic; (2) oral antiseptic and oral astringent; (3) oral antiseptic and oral demulcent; (4) oral antiseptic and oral mucosal protectant; (5) oral antiseptic, oral anesthetic/analgesic, and oral astringent; (6) oral antiseptic, oral anesthetic/analgesic, and oral demulcent; and (7) oral antiseptic, oral anesthetic/analgesic, and oral mucosal protectant. (See section I.L., comment 29.)

6. The agency is proposing to revise the statement of identity in § 356.51(a) of the Panel's recommended monograph (and including the revised statement in § 356.64(a) of this tentative final monograph) as follows: "The labeling of the product contains the established name of the drug, if any, and identifies the product as an 'oral antiseptic,' or an 'antiseptic' (select one of the following: 'rinse,' 'gargle,' or 'rinse and gargle')." (See section I.K., comments 20 and 21.)

7. The agency is proposing the following indication in § 356.64(b) of this tentative final monograph: "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" or "bacterial contamination") "in" (select any of the following: "minor cuts," "minor scrapes," or "minor oral irritation") (which may be followed by) "caused by" (select any of the following: "dental procedures," "dentures," "orthodontic appliances," or "accidental injury"). (See section I.K., comment 22.)

8. The agency is proposing to replace the Panel's recommended warnings in § 356.51(c)(1)(i) and (c)(1)(ii) with the following warning found in § 356.64(c) of this document: "Do not use this product for more than 7 days unless directed by a dentist or doctor. If sore mouth symptoms do not improve in 7 days, if irritation, pain, or redness persists or worsens, or if swelling, rash, or fever develops, see your dentist or doctor promptly." (See section I.K., comment 25.)

9. The agency is proposing professional labeling in § 356.80 for the use of povidone-iodine as a dental preoperative preparation by health care professionals. (See section I.K., comment 27.)

10. The agency has determined that, because the final formulation of an oral antiseptic drug product can affect the effectiveness of the active ingredient, final formulation testing of oral health care antiseptic drug products is necessary. Therefore, the agency is proposing final formulation testing procedures be included in this tentative final monograph. These testing procedures are being put forth for comment in this document.

The Panel recommended that evidence be submitted to verify that each antiseptic ingredient is released from its vehicle when applied to mucous membranes, but it did not include final formulation testing procedures for OTC oral antiseptics in its recommended monograph (47 FR 22760 at 22890). The agency, however, is aware that the final formulation of an oral health care drug product can affect the activity of an antiseptic ingredient included in that product. Therefore, in keeping with the final formulation testing procedures proposed for first aid antiseptic drug products (i.e., those applied to the skin) (56 FR 33644 at 33673) and those that will be proposed for health care antiseptic drug products (e.g., surgical scrubs) in a future issue of the **Federal Register**, the agency is proposing procedures for testing the final formulations of oral health care antiseptic drug products in this tentative final monograph. These testing procedures are based upon the in vitro effectiveness testing procedures recommended by the Oral Cavity Panel (47 FR 22760 at 22890 to 22893) and the first aid antiseptic testing procedures proposed by the agency in § 333.70 of the tentative final monograph for OTC first aid antiseptic drug products (56 FR 33644 at 33673). In general, the proposed testing procedures for first aid antiseptic drug products have been modified to account for the different test organisms required for testing the effectiveness of oral antiseptics. The agency has also taken into account all

comments pertaining to the Oral Cavity Panel's recommended in vitro testing guidelines. (See section I.M., comments 34 and 35.)

In the testing procedures included in the tentative final monograph for OTC first aid antiseptic drug products, the agency proposed in § 333.70(b)(2)(i) and (b)(2)(ii) a "neutralizer inactivation of antiseptic test" and a "neutralizer effect on bacterial viability test" (56 FR 33644 at 33678 and 33679). Differences in microbial plate counts greater than 20 percent between test and control cultures require that the overall test results be discarded. Based upon new information, the agency is concerned that a 20-percent difference in microbial plate counts might be too restrictive. There is a relatively large inherent variation in microbial plate counts. In addition, because the criterion for fulfilling the requirements of the overall testing procedures is a 3-$\log_{10}$ reduction in viable organisms (i.e., 99.9 percent), the agency now questions whether a 1-$\log_{10}$ (i.e., 90 percent) difference might not be a more reasonable criterion for the differences in microbial plate counts for the neutralizer tests. Although the agency is proposing the 20-percent criterion in this tentative final monograph for consistency with the OTC first aid antiseptic tentative final monograph, the agency requests comment on this matter.

In addition, in § 333.70(c)(5) of the OTC first aid antiseptic tentative final monograph, the agency proposed a "test organism antiseptic resistance test" in which the test organisms' resistance to phenol is determined in order to ensure that the resistance of each organism to antiseptics has not changed (56 FR 33679). The Oral Cavity Panel recommended that a 0.2-percent chlorhexidine gluconate solution be used as a positive control to assure the consistent susceptibility of the test organisms (47 FR 22760 at 22891). However, the agency believes that determining an organism's resistance or lack of resistance to phenol or chlorhexidine gluconate has no bearing upon whether or not that organism's susceptibility to a particular test ingredient has changed. The mechanism of action of the test antiseptic may be quite different than that of phenol or chlorhexidine gluconate. Because the "test organism antiseptic resistance test" is designed to demonstrate that the active ingredient is still active in the specific formulation under test, and the active ingredient has presumably already been shown to have in vitro and in vivo antiseptic activity by itself, the proper control is the active ingredient alone. Therefore, the agency is suggesting that the active ingredient, in a suitable inactive medium, be used as a positive control.

The complete testing procedures are included in § 356.90 of this tentative final monograph. The agency invites specific comment at this time on the final formulation testing procedures proposed in this document. 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 testing procedures may need to be revised periodically as newer techniques are developed and proven adequate.

11. For an active ingredient to be included in an OTC drug final monograph, in addition to information demonstrating safety and effectiveness, it is necessary to have publicly available sufficient chemical information that can be used by all manufacturers to determine that the ingredient is appropriate for use in their products. Only some of the oral antiseptic active ingredients that the Panel evaluated are standardized and characterized for quality and purity and are included in official compendia. Alcohol, benzalkonium chloride, benzethonium chloride, benzoic acid, boric acid, camphor, carbamide peroxide, cetylpyridinium chloride, cresol, gentian violet, hydrogen peroxide, iodine, menthol, methyl salicylate, nitromersol, oxyquinoline sulfate, phenol, povidone-iodine, tolu balsam, and thymol are currently included as articles in the U.S.P. (Ref. 1). The remaining oral antiseptic active ingredients are not adequately characterized and would need to be if data are submitted to upgrade them to monograph status.

The agency believes that it would be appropriate for parties interested in upgrading nonmonograph ingredients to monograph status to develop with the United States Pharmacopoeial Convention appropriate standards for the quality and purity of any of these ingredients that are not already included in official compendia. Should appropriate standards fail to be established, ingredients otherwise eligible for monograph status will not be included in the final monograph.

Reference

(1) "United States Pharmacopeia XXII—National Formulary XVII," United States Pharmacopeial Convention, Inc., Rockville, MD, pp. 34, 146, 149, 219–220, 223, 268, 605, 663, 703–703, 821–822, 954, 1061, 1119, 1390, 1904–1905, 1906, 1921–1922, 1947–1948, 1955, 1991, 1989.

The agency has examined the economic consequences of this proposed rulemaking and has determined that it does not require either a regulatory impact analysis, as specified in Executive Order 12866, or a regulatory flexibility analysis, as defined in the Regulatory Flexibility Act (Pub. L. 96–354). This rulemaking for OTC oral antiseptic drug products is not expected to have an impact on small businesses.

This proposed rule does not include any Category I ingredients. Some ingredients are in Category II (not generally recognized as safe and effective), but most are in Category III (more data needed to establish safety and effectiveness). If data are not submitted to upgrade these ingredients to monograph status, OTC products containing oral antiseptics will not bepermitted to display antiseptic drug claims in labeling. However, most of these products could remain in the marketplace. After relabeling, many products could be marketed as cosmetics; others could be marketed as OTC oral wound cleansing drug products. After reformulation and relabeling, a few products could be sold as OTC oral anesthetic/analgesics. Many OTC products containing oral antiseptics are labeled for use to reduce or prevent the accumulation of dental plague. Unless a safety concern arises, such products may remain on the market until the agency's evaluation of antiplaque and antiplaque-related products is completed.

The impact of the proposed rule, if implemented, appears to be minimal. Therefore, the agency concludes that the proposed rule is not a major rule as defined in Executive Order 12866. Further, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act.

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC oral antiseptic drug products. No comments on economic impacts were received.

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC oral antiseptic drug products. Comments regarding the impact of this rulemaking should be accompanied by appropriate documentation. 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 August 8, 1994, submit to the Dockets Management Branch (address above) 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 August 8, 1994. 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 February 9, 1995, 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 April 10, 1995. 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. 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 (*insert date 14 months after date of publication in the* Federal Register). Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the Federal Register, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 356

Labeling, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 356 (as proposed in the Federal Register of May 25, 1982 (47 FR 22760), the Federal Register of January 27, 1988 (53 FR 2436), and the Federal Register of September 24, 1991 (56 FR 48302)) be amended as follows:

PART 356—ORAL HEALTH CARE DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for 21 CFR part 356 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. Section 356.3 is amended by adding new paragraphs (m) and (n) to read as follows:

§ 356.3 Definitions.

* * * * *

(m) *Antiseptic drug.* In accordance with section 201(o) of the Federal Food, Drug, and Cosmetic 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."

(n) *Oral antiseptic.* An antiseptic-containing drug product applied topically to the oral cavity to help prevent infection in wounds caused by minor oral irritations, cuts, scrapes, or injury following minor dental procedures.

3. New § 356.11 is added to subpart B to read as follows:

§ 356.11 Antiseptics.

Povidone-iodine provided to health professionals (but not to the general public).

4. Section 356.26 is amended by adding new paragraphs (i), (j), (k), (l), (m), (n), and (o) to read as follows:

§ 356.26 Permitted combinations of active ingredients.

* * * * *

(i) Any single oral antiseptic active ingredient identified in § 356.11 may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.12.

(j) Any single oral antiseptic active ingredient identified in § 356.11 may be combined with any single oral astringent active ingredient identified in § 356.14.

(k) Any single oral antiseptic active ingredient identified in § 356.11 may be combined with any single oral demulcent active ingredient identified in § 356.18.

(l) Any single oral antiseptic active ingredient identified in § 356.11 may be combined with any single oral mucosal protectant active ingredient identified in § 356.20.

(m) Any single oral antiseptic active ingredient identified in § 356.11 may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.12 and any single oral astringent active ingredient identified in § 356.14.

(n) Any single oral antiseptic active ingredient identified in § 356.11 may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.12 and any single oral demulcent active ingredient identified in § 356.18.

(o) Any single oral antiseptic active ingredient identified in § 356.11 may be combined with any single oral anesthetic/analgesic active ingredient identified in § 356.12 and any single oral mucosal protectant active ingredient identified in § 356.20.

5. New § 356.64 is added to subpart C to read as follows:

§ 356.64 Labeling of oral 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 an "oral antiseptic," or an "antiseptic" (select one of the following: "rinse," "gargle," or "rinse and gargle").

(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" or "bacterial contamination") "in" (select any of the following: "minor cuts," "minor scrapes," or "minor oral irritation") (which may be followed by) "caused by" (select any of the following: "dental procedures," "dentures," "orthodontic appliances," or "accidental injury").

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings": "Do not use this product for more than 7 days unless directed by a dentist or doctor. If sore mouth symptoms do not improve in 7 days, if irritation, pain, or redness persists or worsens, or if swelling, rash, or fever develops, see your dentist or doctor promptly."

(d) *Directions.* [Reserved]

6. Section 356.66 is amended by adding new paragraphs (b)(3), (b)(4), (b)(5), (b)(6), (b)(7), (b)(8), (b)(9), (c)(1), (c)(2), (c)(3), and (c)(4) to read as follows:

§ 356.66 Labeling of combination drug products.

* * * * *

(b) * * *

(3) *For permitted combinations identified in § 356.26(i).* In addition to any or all of the indications in § 356.64(b), any or all of the indications in § 356.52(b)(3), (b)(4), and (b)(5) should be used.

(4) *For permitted combinations identified in § 356.26(j).* In addition to any or all of the indications in § 356.64(b), the following indication for oral astringent active ingredients should be used: "For temporary relief of occasional minor irritation, pain, and sore mouth."

(5) *For permitted combinations identified in § 356.26(k).* In addition to any or all of the indications in § 356.64(b), the following indication for oral demulcent active ingredients should be used: "For temporary relief of minor discomfort and protection of irritated areas in sore mouth."

(6) *For permitted combinations identified in § 356.26(l).* In addition to any or all of the indications in § 356.64(b), any or all of the indications in § 356.60(b)(1), (b)(2), and (b)(3) should be used.

(7) *For permitted combinations identified in § 356.26(m).* In addition to any or all of the indications in § 356.64(b), any or all of the indications in § 356.52(b)(3), (b)(4), and (b)(5) should be used. The following indication for oral astringent active ingredients should be used: "For temporary relief of occasional minor irritation, pain, and sore mouth."

(8) *For permitted combinations identified in § 356.26(n).* In addition to any or all of the indications in § 356.64(b), any or all of the indications in § 356.52(b)(3), (b)(4), and (b)(5) should be used. The following indication for oral demulcent active ingredients should be used: "For temporary relief of minor discomfort and protection of irritated areas in sore mouth."

(9) *For permitted combinations identified in § 356.26(o).* In addition to any or all of the indications in § 356.64(b), any or all of the indications in § 356.52(b)(3), (b)(4), and (b)(5) and in § 356.60(b)(1), (b)(2), and (b)(3) should be used.

(c) * * *

(1) *For permitted combinations identified in § 356.26(i).* In addition to the warnings in § 356.64(c), the warnings in § 356.52(c)(2), (c)(3), and (c)(4), if applicable, should be used.

(2) *For permitted combinations identified in § 356.26(j).* The warnings in § 356.64(c) should be used.

(3) *For permitted combinations identified in § 356.26(k).* The warnings in § 356.64(c) should be used.

(4) *For permitted combinations identified in § 356.26(k).* In addition to the warnings in § 356.64(c), the warnings in § 356.52(c)(2), (c)(3), and (c)(4), if applicable, should be used.

7. Section 356.80 is amended by adding new paragraph (d) to read as follows:

§ 356.80 Professional labeling.

* * * * *

(d) The labeling of aqueous products containing povidone-iodine identified in § 356.11 provided to health professionals (but not to the general public) may contain the following:

(1) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as an "oral antiseptic," or an "antiseptic" (select one of the following: "rinse," "gargle," or "rinse and gargle").

(2) *Indications.* The labeling of the product states under the heading "Indications," the following: "For preparation of the oral mucosa prior to injection, dental surgery, or tooth extraction."

(3) *Directions.* The labeling of the product contains the following information under the heading "Directions:" For products containing povidone-iodine identified in § 356.11, the final product to be applied is a 0.5 percent aqueous solution. Manufacturers may also market a more concentrated solution provided that it contains adequate directions to dilute the product to a 0.5 percent aqueous solution. "Apply 10 to 20 milliliters of solution to the operative site. Instruct the patient to rinse for 30 seconds and then spit out. Wait 2 minutes, and apply another 10 to 20 milliliters of solution to the operative site. Instruct the patient to rinse again for 30 seconds and then spit out. With a standard syringe and a blunt, angulated needle, irrigate the operative site and the surrounding gingival mucosa for 1 minute with 10 to 20 milliliters of the solution. Instruct the patient to spit out the solution after the irrigation procedure."

8. New subpart D consisting of § 356.90 is added to read as follows:

Subpart D—Final Formulation Testing Procedures

§ 356.90 Testing of oral antiseptic drug products.

An oral antiseptic drug product in a form suitable for topical application will be recognized as effective if it contains an active ingredient included in § 356.11 and if, at its lowest recommended use concentration, it decreases the number of bacteria per milliliter in *Streptococcus mutans* (ATCC No. 25175), *Actinomyces viscosus* (ATCC No. 19246), and *Candida albicans* (ATCC No. 18804) cultures (available from American Type Culture Collection (ATCC), 12301 Parklawn Dr., Rockville, MD 20852) by 3 $\log_{10}$ within 10 minutes at 37 °C in the presence of 10 percent serum in vitro. Oral antiseptic drug products 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 serum reagent—(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 X 100 millimeters. Use covers of suitable material.

(3) *Serum Reagent*—Use inactivated fetal bovine serum without added preservatives and/or antiinfective products.

(b) *Culture media and diluting fluids*—(1) Culture media. Use Brain Heart Infusion Medium for culture media and diluting fluids. Prepare the medium as follows:

	Brain Heart Infusion Medium
Calf Brain, infusion from	200 grams
Beef Heart, Infusion from	250 grams
Peptone	10 grams
Sodium chloride	5 grams
Disodium phosphate	2.5 grams
Dextrose	2 grams
Water, distilled	q.s. to 1,000 milliliters

Mix thoroughly. Heat with frequent agitation and boil for 1 minute. Sterilize by autoclaving at 121 °C for 15 minutes. 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 the medium will have a final pH of 7.4 after sterilization.

(i) *Medium A (without neutralizers).* Use Brain Heart Infusion medium corresponding to that described in paragraph (b)(1) of this section.

(ii) *Medium B.* Brain Heart Infusion agar medium. Same as Medium A, except for the addition of 15 grams of agar per liter.

(iii) *Medium C.* Same as diluting fluid 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.

(2) *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.

(3) *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 37 °C by incubating appropriate volumes of all solutions in a water bath at 37 °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 37 °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)(1)(i) of this section, and in the appropriate diluting fluid (neutralizing medium), specified in paragraph (b)(2) 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)(1)(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.

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

(i) *Streptococcus mutans* (ATCC No. 25175).

(ii) *Actinomyces viscosus* (ATCC No. 19246).

(iii) *Candida albicans* (ATCC No. 18804).

(2) *Preparation of suspension.* Maintain stock cultures on Medium B agar slants by monthly transfers. Alternatively, cultures may be lyophilized and stored at -70 °C. Incubate new stock transfers 2 days at 37 °C; then store at 2 to 5 °C. Incubate *Streptococcus mutans* and *Actinomyces viscosus* anaerobically. Incubate *Candida albicans* aerobically. 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 37 °C, before using the culture for testing. Use a 16- to 18-hour culture of *Streptococcus mutans* and *Candida albicans* and a 32- to 36-hour culture of *Actinomyces viscosus* grown in Medium A at 37 °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 109 cells per milliliter.

(4) *Plate-count assay.* For each culture to be assayed, pipet 1.0 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 37 °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 ensure that antiseptic resistance properties of each organism have not changed substantially, determine the

susceptibility of each organism to the active ingredient(s) being tested, in a suitable inactive medium, using the testing procedures in this section. The organisms are satisfactory if the number of organisms per milliliter are reduced by 3 $\log_{10}$ within 10 minutes at 37 °C in the presence of 10 percent serum.

(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)(2)(i) and (b)(2)(ii) of this section or that can be overcome by dilution.

(ii) *Bactericidal assay procedure.* Prewarm all test solutions by incubating appropriate volumes at 37 °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 the test antiseptic product at its recommended use concentration into a medication tube and mix well. Incubate at 37 °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 37 °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 the test antiseptic product 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 37 °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.

Dated: December 10, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

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