(ii) The State agency shall mail the monthly report form to the household along with the notice of expiration.

(iii) The household shall submit the monthly report to the State agency in accordance with paragraph (i)(1) of this section.

(iv) The State agency shall deliver the recertification addendum to the household along with the monthly report form or obtain the necessary information from the household at the interview.

(v) The household shall submit the addendum to the State agency no later than the time of the interview.

(5) *Interview.* (i) The State agency shall conduct a complete interview with a household member or an authorized representative.

(ii) The State agency shall schedule the interview at any time during the last month of the old certification period.

(iii) If the State agency schedules the interview for a date on or before the normal filing due date of the monthly report, the State agency shall permit the household member and authorized representative to bring the recertification form or monthly report to the interview.

* * * * *

(91 Stat. 958 (7 U.S.C. 2011–2029))

(Catalogue of Federal Domestic Assistance Programs No. 10.551, Food Stamps)

Dated: May 18, 1982.

Mary Jarratt,

Assistant Secretary.

[FR Doc. 82–14088 Filed 5–24–82; 8:45 am]

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Tuesday
May 25, 1982

Part IV

Department of Agriculture

Food and Nutrition Service

Determining Eligibility for Free and Reduced Price Meals and Free Milk in Schools; Revised Application Procedures and Verification of Eligibility; Proposed Rules

DEPARTMENT OF AGRICULTURE

Food and Nutrition Service

7 CFR Part 245

Determining Eligibility for Free and Reduced Price Meals and Free Milk in Schools; Revised Application Procedures

AGENCY: Food and Nutrition Service, USDA.

ACTION: Proposed rule.

SUMMARY: This proposed rule would implement the following changes required by the Omnibus Budget Reconciliation Act of 1981 (Pub. L. 97–35): (1) Require additional information on applications for free and reduced price benefits in the National School Lunch, Commodity School, School Breakfast and Special Milk Programs; (2) require schools to include in their letters to parents only the *reduced price* Income Eligibility Guidelines for meals (schools participating only in the Special Milk Program must include the *free* Guidelines and public releases would still contain both Guidelines); (3) require schools to distribute applications to parents of children in attendance at school; and (4) remove both the hardship and standard deductions and the restriction that School Food Authorities may verify the information on the application solely "for cause". This rule will reduce program abuse and will result in a savings of Federal funds.

DATE: To be assured of consideration comments must be postmarked on or before June 24, 1982. Since this proposal is one of two proposals regarding the provisions of section 803 of Pub. L. 97–35, commentors should clearly indicate that comments reference the proposed rule "Revised Application Procedures".

ADDRESSES: Comments should be sent to Stanley C. Garnett, Branch Chief, Policy and Program Development Branch, School Programs Division, Food and Nutrition Service, USDA, Alexandria, Virginia 22302. All written submissions will be available for public inspection in Room 509, 3101 Park Center Drive, Alexandria, Virginia 22302, during regular business hours (8:30 a.m. to 5:00), Monday through Friday.

FOR FURTHER INFORMATION CONTACT: Stanley C. Garnett, at the address listed above.

SUPPLEMENTARY INFORMATION:

Classification

This proposed action has been reviewed under Executive Order 12291 and has been classified *not major.* We do not anticipate that this proposal will have an impact on the economy of more than $100 million. The proposed rule is intended to ensure that free and reduced price benefits are directed to only those children from families whose income fall within the Income Eligibility guidelines set forth by the Department by household size. No major increase in cost or prices for program participants; individual industries; Federal, State or local government agencies; or geographic regions is anticipated. This proposal is not expected to have significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based enterprises to compete with foreign-based enterprises in domestic or foreign markets.

This proposal has also been reviewed with regard to the requirements of Pub. L. 96–354, the Regulatory Flexibility Act. Samuel J. Cornelius, Administrator of the Food and Nutrition Service, has certified that this proposed rule does not have a significant economic impact on State agencies and local School Food Authorities.

In accordance with the Paperwork Reduction Act of 1980 (Pub. L. 96–511), the reporting and recordkeeping requirements contained in this proposed rule will be submitted to the Office of Management and Budget for approval. They are not effective until OMB approval has been obtained.

Samuel J. Cornelius has determined that an urgent need exists to limit the comment period to 30 days since the provisions of this rule directly affect the application process for school year 1982–83. Most States and School Food Authorities print their applications during the summer months in order to have applications prepared for the start of the school year in August or September. In order to meet these timeframes, an interim rule must be in place no later than July, thus necessitating the short comment period. The Department intends to solicit additional public comment on the forthcoming interim rule which will be effective for School Year 1982–83.

Background

Section 9 of the National School Lunch Act (Act) contains a provision that lunches be served free or at a reduced price to children who are unable to pay the full price of a lunch. Prior to Pub. L. 97–35, local school officials were required to determine eligibility for free and reduced price meals "solely on the basis of an affidavit executed in such form as the Secretary may prescribe by an adult member of such household." Regulations implementing section 9 require that the affidavit (application) request only that information necessary to determine eligibility, namely family size and family income. In order to determine eligibility school officials were directed to compare the Income Eligibility Guidelines issued by the Secretary to the family size and income information furnished by the parent.

Previously, section 9 of the Act also provided that school officials "may for cause seek verification of the data in such application." The "for cause" provision limited verification to those situations where school officials had actual cause to believe the information on the application was erroneous.

Changes Due to Public Law 97–35

In an effort to control Federal spending, curtail abuse, and direct Federal benefits to the most needy, Congress made fundamental changes in the child nutrition programs. Many of these changes affect the free and reduced price application process. Section 803 of the Omnibus Budget Reconcilation Act of 1981 (Pub. L. 97–35) amended section 9 of the National School Lunch Act (Act) to implement these changes. These changes require:

(1) The applicant to furnish the social security numbers of all adult household members on the free and reduced price application;

(2) Appropriate documentation of income or documentation showing that the household is participating in the Food Stamp Program;

(3) Only the reduced price guidelines be included in the letter to parents with an explanation that households with income less than or equal to the reduced price guidelines are eligible for either free or reduced price meals;

(4) Schools to distribute applications to the parents of children in attendance at school;

(5) The elimination of hardship provisions and standard deductions;

(6) The elimination of the restriction that allowed verification by School Food Authorities solely "for cause";

(7) The Department to conduct a pilot study on income verification; and

(8) That the household's annual income at the time of application be considered in the eligibility determination.

Departmental Response

In response to the provisions of section 803, Pub. L. 97–35, the Department is publishing two proposed rules.

This proposal, Revised Application Procedures, is primarily intended to

address those provisions of section 803 affecting the application process at the beginning of the school year. Many of these provisions are nondiscretionary. Normally the Department would publish nondiscretionary provisions as a final rule since public comment is unnecessary. However, this rule contains several ancillary provisions which are subject to Departmental discretion. For this reason, the Department intends to provide a 30-day comment period. This will enable the Department to analyze the comments and publish an interim rule in sufficient time to affect the 1982–83 application process.

The second proposal, Verification of Eligibility, is designed to address the verification-related provisions of section 803. A 60-day public comment period will be provided. Based on an analysis of public comments, the Department intends to set forth an interim rule early next school year for implementation during the school year.

Comments will be accepted for both interim rules. One final rule incorporating all provisions of section 803, Pub. L. 97–35 will be developed following an analysis of comments received.

This Proposed rule will implement the following changes to the free and reduced price application process in response to section 803 as follows: (Comments are solicited on those areas where the Department is able to make revisions, as described at the end of the preamble.)

(1) *Requires additional information on free and reduced price applications.* This rule proposes to revise Part 245 to expand the information required on the free and reduced price application. As required by section 803 of Pub. L. 97–35, the applicant must provide the social security numbers of all adult household members in order for the application to be considered for benefits. For purposing to define "adult" as an individual who is 21 years of age or older. Further, the Department proposes to define "household" as "family" (§ 245.2(b)).

To reduce program abuse, section 803(b) also amended section 9 of the Act to require the Secretary to prescribe adequate documentation of eligibility for benefits. The Department proposes to define documentation as completion of the following information on the application: (1) Total household income; (2) names of all household members; (3) social security numbers of all adult household members, or an indication that application for one has been made or in the case of aliens ineligible for social security numbers, an indication that none can be acquired; and (4) signature of the parent or legal guardian. This approach is intended to maintain the existing application process, thus limiting the burden on the applicant as well as on the school official. These are Federal minimums; State agencies and local School Food Authorities may require households to provide additonal information to establish eligibility for free and reduced price benefits. This proposed rule would further expand the information required on the application by including a question regarding household participation in the Food Stamp Program. This will assist in the verification process as explained in the proposed rule, Verification of Eligibility.

These provisions will affect the first performance standard of the Assessment, Improvement, and Monitoring System (AIMS). That standard requires that each child's application for free and reduced price benefits is correctly approved or denied. Prior to Pub. L. 97–35, applications were deemed complete if the total number of family members, total family income, and the parent's or guardian's signature were provided. This proposal would change the requirements for a complete application to include: (1) Social security information; (2) total household income; (3) names of all household members; and (4) the signature of the parent or legal guardian.

Commentors should be aware that the provision of information required on a free and reduced price application would be considered a condition of eligibility, as required by Pub. L. 97–35. As a result, State agencies must ensure that all School Food Authorities obtain the information prescribed by the Secretary. Applications which do not contain such information will be considered incomplete and therefore insufficient to substantiate the receipt of Federal funds. The State agency or School Food Authority must also deny benefits if the information on the application establishes ineligibility or is incomplete, and shall not claim special assistance reimbursement based on such application. The School Food Authority must notify the household in writing of a denial of benefits. The notice must advise the household of the denial and of the right to a fair hearing. The reasons for ineligibility must be properly documented and must be retained on file at the School Food Authority.

Section 7 of the Privacy Act of 1974 requires any Federal, State, or local government agency which requests an individual to disclose his or her social security number, to inform the individual whether the disclosure is mandatory or voluntary, by what authority the number is solicited, and what uses will be made of it. In this regard, the Department's Office of Inspector General intends to use social security numbers to verify income information on a sample of applications. In order to comply with section 7, the application for free and reduced price benefits must indicate that section 9 of the National School Lunch Act, as amended, requires the social security numbers of all adult household members as a condition of eligibility. In addition, the application must indicate that the social security number(s) may be used to verify the information on the application and that failure to provide the required social security information will lead to the denial of benefits.

Under this proposal, the letter or notice to parents must indicate that a completed application is a condition of eligibility for free and reduced price meals. In addition, the letter to parents must indicate that all households with children receiving free and reduced price benefits must notify the appropriate school officials of changes in household size or increases in income of over $25 per month.

(2) *Requires schools to include in their letter to parents only the reduced price Income Eligibility Guidelines,* and an explanation that households with income equal to or less than the reduced price guidelines are eligible for either free or reduced price meals. Schools participating in the Special Milk Program, where the School Food Authority exercises its option to serve free milk, must send home the free Guidelines. Public releases would continue to contain both Guidelines.

(3) *Requires schools to distribute applications to parents of children in attendance at school.* Existing program regulations already require schools to distribute applications to parents of children in attendance at school. At School Food Authority discretion, applications may be mailed or handed out in classrooms and carried home by students.

(4) *Eliminates the hardship provisions and standard deductions.* From 1973 until the passage of Pub. L. 96–499, the Department allowed a family to deduct from its stated income the cost of certain "hardships" that the family could not reasonably anticipate or control. Last school year, Pub. L. 96–499 established a standard deduction to offset the removal of hardship deductions. This school year, section 803 of Pub. L. 97–35 permanently removes both hardship provisions and standard deductions.

(5) *Eliminates the "for cause" restriction.* State agencies and School Food Authorities are now authorized under section 9(b)(2)(C) of the Act, as amended, to verify the information on the application at their discretion.The Department proposes that State agencies or School Food Authorities doing so must ensure that verification is applied without regard to race, sex, color, national origin, age or handicap. In today's **Federal Register,** the Department proposes the "Verification of Eligibility" rule to implement several verification related provisions of section 803. That proposal sets forth the Department's requirements concerning the verification of information on the application, notification of adverse action, and continuation of benefits.

(6) *Exempts pilot projects.* Section 803 of Pub. L. 97–35 also requires the Department to conduct a pilot study on verification. Schools that participate in that study will be instructed by the Department on the use of specific application forms, documentation, and techniques for verification of eligibility information.

The pilot study will utilize several different application and verification methods starting this school year. The available results of the pilot study will be carefully evaluated by the Department and will be used in the development of the final rules.

(7) *Requires use of current income.* In the past, schools could consider either the family's current rate of income or the family's income during the past 12 months to determine eligibility for free and reduced price meals.

Section 803 of Pub. L. 97–35 states that "any child who is a member of a household whose income, at the time the application is submitted, is at an annual rate which does not exceed the applicable family size income level" is eligible to receive free or reduced price meals. The Department proposes to define "current income" as income at the time of application, if representative, and annualized. Current income would be determined based on the income received during the month prior to application and multiplied by 12, if such income is representative, or income received during the past 12 months in the case of farmers, the self-employed, migrant workers, or others if the past 12 months are more representative.

Recordkeeping

In addition to the above mentioned changes, the Department proposes to require State agencies to maintain records demonstrating compliance with all of the requirements of this proposal, and proposes to monitor for compliance during the management evaluation process.

Solicitation of Comments

The Department exercised its authority in the following areas and solicits comments thereon: (1) The definitions of "adult", "household", "documentation", and "current income"; (2) Requiring that verification be applied without regard to race, sex, color, national origin, age or handicap; (3) allowing schools involved in the pilot study to deviate from routine application and verification procedures; (4) Including on the application a question regarding food stamp participation for purposes of simplifying the verification process later in the school year; (5) Requiring households to report changes in circumstances; and (6) Requiring School Food Authorities to notify households of the denial of benefits.

List of Subjects in 7 CFR Part 245

Food assistance programs, Grant programs—social programs, National School Lunch Program, School Breakfast Program, Special Milk Program, Reporting and recordkeeping requirements.

PART 245—DETERMINING ELIGIBILITY FOR FREE AND REDUCED PRICE MEALS AND FREE MILK IN SCHOOLS

Accordingly, Part 245 is proposed to be amended as follows:

(1) In § 245.1 paragraph (a) is revised to read as follows:

§ 245.1 General purpose and scope.

(a) This part establishes the responsibilities of State agencies, Food and Nutrition Service Regional Offices (where applicable), and School Food Authorities in providing free and reduced price meals and free milk in the National School Lunch Program (7 CFR Part 210), the School Breakfast Program (7 CFR Part 220), the Special Milk Program for Children (7 CFR Part 215), and commodity schools. Section 9 of the National School Lunch Act, as amended, and Sections 3 and 4 of the Child Nutrition Act of 1966, as amended, require schools participating in any of the programs and commodity schools to make available, as applicable, free and reduced price lunches, breakfasts, and, at the option of the School Food Authority for schools participating only in the Special Milk Program, free milk to eligible children.

* * * * *

(2) In § 245.2 definition (a) "Commodity only school" is redesignated as (a–1). New definitions (a) "Adult", (a–2) "Current income", and (d–2) "Household" are added.

§ 245.2 Definitions.

(a) "Adult" means any individual 21 years of age or older.

* * * * *

(a–2) "Current income" means income, as defined in § 245.6(a), received during the month prior to application, if representative, and multiplied by 12, or for farmers, self-employed persons, migrant workers, or other income received during the past 12 months, if more representative.

* * * * *

(d–2) "Household" means "family" as defined in § 245.2(b).

* * * * *

(3) In § 245.2, definition (e) "Income poverty guidelines" is amended by removing the word "poverty" and inserting in its place the word "eligibility."

(4) In § 245.3, paragraph (a) the last sentence is revised to read as follows:

§ 245.3 Eligibility standards and criteria.

(a) * * * Such family size income standards for free and reduced price meals and for free milk shall be in accordance with Income Eligibility Guidelines published by the Department by notice in the **Federal Register.**

* * * * *

(5) In § 245.3, paragraph (c) the second sentence is removed.

(6) Section 245.3 is amended by removing paragraph (d) in its entirety. That paragraph contained instructions to implement Public Law 96–499 and the paragraph is now obsolete.

(7) In § 245.5(a)(1), paragraphs (i), (ii) and (vi) are revised to read as follows. The period ending paragraph (vii) is removed and replaced with a semi-colon. New paragraphs (viii) and (ix) are added.

§ 245.5 Public announcement of the eligibility criteria.

* * * * *

(a)(1) * * * (i) The Income Eligibility Guidelines for *reduced price* meals with an explanation that households with incomes less than or equal to the reduced price criteria would be eligible for free or reduced price meals (the Income Eligibility Guidelines for free meals shall *not* be included in letters or notices to such applicants unless the applicant is applying for benefits in the Special Milk Program); (ii) an explanation that the information on the application may be verified at any time during the school year; * * * (vi) the statement: "In the operation of child feeding programs, no child will be

discriminated against because of race, sex, color, national origin, age, or handicap"; * * * (viii) an explanation that recipients of free and reduced price benefits must notify the appropriate school officials of any changes during the school year in family size and increases in level of income which exceed $25 per month; and (ix) an explanation that a completed and signed application is a prerequisite to be considered for free and reduced price benefits.

* * * * *

(9) Section 245.6(a) is amended as follows:

(a) In § 245.6(a) the introductory paragraph is amended by adding the word "current" between the words "with respect to the" and "annual income of" in the third sentence and by revising the phrase at the end of the introductory paragraph as set forth below.

(b) Paragraph (a) is further amended by revising paragraph (a)(1) and the first two sentences of paragraph (a)(2) as set forth below, and by removing the phrase "for cause" from the third sentence of paragraph (a)(2).

§ 245.6 Application for free and reduced price meals and free milk.

(a) * * * The application shall require applicants to provide the social security number of all household members 21 years of age or older, an indication that application for one has been made or in the case of aliens ineligible for social security numbers, an indication that none can be acquired. The application shall contain substantially the following statements; (1) "In certain cases foster children are eligible for free or reduced price meals or free milk regardless of your family income. If you have such children living with you and wish to apply for such meals or milk for them, please contact us." and (2) "Section 9 of the National School Lunch Act requires that the social security number of each adult household member be given as a condition of eligiblity. The social security numbers may be used for verification of the information on the application. Failure to provide social security number information shall result in a denial of benefits." In addition the application must enable the applicant to indicate whether the household is participating in the Food Stamp Program. * * *

* * * * *

(10) In § 245.6, paragraph (b) is revised to read as follows and new paragraph (b–1) is added.

* * * * *

(b) *Determination of eligibility.* When a completed application furnished by a family indicates that the family meets the eligibility criteria for free or reduced price meals or free milk, the children from that family shall be provided the benefits to which they are entitled. School officials may seek verification of the information on the application. When the information furnished by the family is not complete or does not meet the eligibility criteria for free or reduced price benefits, school officials shall provide written notice to each family denied benefits. At a minimum, this notice shall include: (1) The reason for the denial of benefits, e.g. income in excess of allowable limits or incomplete application; (2) notification of the right to appeal; (3) instructions on how to appeal; and (4) a statement reminding parents that they may reapply for free and reduced price benefits at any time during the school year. The reasons for ineligibility shall be properly documented and retained on file at the School Food Authority, as appropriate.

(b-1) *Appeals of denied benefits.* A family who wishes to appeal a denied application by the School Food Authority shall do so under the hearing procedures established under § 245.7. However, prior to initiating the hearing procedure, the parent may request a conference to provide the opportunity for the parent and school officials to discuss the situation, present information, and obtain an explanation of the data submitted in the application or the decision rendered. The request for a conference shall not in any way prejudice or diminish the right to a fair hearing. The School Food Authority must promptly schedule a fair hearing, if requested.

* * * * *

(11) In § 245.6, an new paragraph (d) is added to read as follows:

§ 245.6 Application for free and reduced price meals and free milk.

* * * * *

(d) School Food Authorities which are involved in the Department's pilot study on income verification may be exempted from the requirements of this section and shall obtain verification and documentation as directed by the Department.

(12) In § 245.10, a new paragraph (f) is added to read as follows:

§ 245.10 Action by School Food Authorities.

* * * * *

(f) School Food Authorities verifying the information on the free and reduced price application shall ensure that verification activities are applied without regard to race, sex, color, national origin, age, or handicap.

(13) In § 245.11, a new paragraph (g) is added to read as follows:

§ 245.11 Action by State agencies and FNSRO's

* * * * *

(g) State agencies or FNSRO's, as applicable, verifying the information on the free and reduced price application shall ensure that verification activities are applied without regard to race, sex, color, national origin, age, or handicap.

(Sec. 803; Pub. L. 97–35; 95 Stat. 521–535; (42 USC 1758))

Signed in Washington, D.C. on May 21, 1982.

John W. Bode,

Deputy Assistant Secretary for Food and Consumer Services.

[FR Doc. 82–14365 Filed 5–24–82; 8:45 am]

BILLING CODE 3410–30–M

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7 CFR Part 245

Determining Eligibility for Free and Reduced Price Meals and Free Milk in Schools; Verification of Eligibility

AGENCY: Food and Nutrition Service, USDA.

ACTION: Proposed rule.

SUMMARY: This rule proposes to amend Part 245 to implement several provisions of section 803 of Pub. L. 97–35, the Omnibus Budget Reconciliation Act of 1981. Under this proposal, minimum standards are established for the verification of the information on applications for free or reduced price meals or free milk benefits served in the National School Lunch, School Breakfast, Commodity School and Special Milk Programs. This proposal is intended to prevent errors and abuse in the delivery of free and reduced price benefits.

DATES: To be assured of consideration, comments must be postmarked on or before July 26, 1982. Since this proposal is one of two proposals regarding the provisions of section 803, commentors should clearly indicate that comments reference the proposed rule, "Verification of Eligibility."

ADDRESSES: Comments should be sent to Stanley C. Garnett, Branch Chief, Policy and Program Development Branch, School Programs Division, Food and Nutrition Service, USDA, Alexandria, Virginia 22302. All written submissions will be available for public inspection in Room 509, 3101 Park Center Drive, Alexandria, Virginia 22302, during regular business hours

(8:30 a.m. to 5:00 p.m.), Monday through Friday.

FOR FURTHER INFORMATION CONTACT:
Mr. Garnett at the address listed above, or call (703) 756–3620.

SUPPLEMENTARY INFORMATION:

Classification

This proposed action has been reviewed under Executive Order 12291 and has been classified *not major*. We do not anticipate that this proposal will have an impact on the economy of more than $100 million. The proposed rule is intended to ensure that free and reduced price benefits are directed to only those children from families whose income fall within the Income Eligibility Guidelines set forth by the Department by household size. No major increase in cost or prices for program participants; individual industries; Federal, State or local government agencies; or geographic regions is anticipated. This proposal is not expected to have significant adverse effects on competition, employment, investment, productivity, innovation, or on the ability of U.S.-based enterprises to compete with foreign-based enterprises in domestic or foreign markets.

This proposal has also been reviewed with regard to the requirements of Pub. L. 96–354, the Regulatory Flexibility Act. Samuel J. Cornelius, Administrator of the Food and Nutrition Service, has certified that this proposed rule does not have a significant economic impact on State agencies and local School Food Authorities.

In accordance with the Paperwork Reduction Act of 1980 (Pub. L. 96–511), the reporting and recordkeeping requirements contained in this proposed rule will be submitted to the Office of Management and Budget for approval. They are not effective until OMB approval has been obtained.

Background

Prior to the passage of Pub. L. 97–35, section 9 of the National School Lunch Act (Act) provided that school officials "may for cause seek verification of the data in such application." The "for cause" provision limited verification to those situations where school officials had actual cause to believe the information furnished on the application was erroneous. For that reason, verification of the information on free and reduced price applications has been an infrequent occurrence.

Section 803 of Pub. L. 97–35 made several changes to the Act which affected the free and reduced price meal or free milk application process. While most of the changes affect the information collected on the application, several changes concern the verification of that information. Specifically, section 803 authorizes the Secretary, States, and local School Food Authorities to seek verification of the data contained in the application. Further, local School Food Authorities are *required* to undertake such verification procedures as may be prescribed by the Secretary, and to make appropriate changes in the eligibility determinations on the basis of such verification.

In response to the provisions of section 803 of Pub. L. 97–35, the Department is publishing two proposed rules.

This proposal, Verification of Eligibility, is designed to emplement the verification provisions of section 803 that do not have an immediate impact on the application process at the beginning of the school year. This proposal addresses the verification of information on free and reduced price applications, the notification to households when benefits are reduced or terminated and State agency recordkeeping requirements. A 60-day public comment period is provided to ensure that the public has sufficient opportunity for comment. Based on an analysis of the comments, the Department intends to publish an interim rule early next school year to allow schools and States to gain operational experience with verification procedures. Comments will be solicited on that interim rule and will be considered in the development of a final rule.

Another proposed rule, Revised Application Procedures (published in today's **Federal Register**), is designed to implement those provisions of section 803 affecting the application process at the beginning of the school year. Many of those provisions are nondiscretionary. Normally, the Department would publish nondiscretionary provisions as a final rule since public comment is unnecessary. However, the Revised Application Procedures rule contains several ancillary provisions which are subject to Departmental discretion. For this reason, the Department intends to provide a 30-day public comment period for that rule. That abbreviated comment period will provide time for the Department to analyze the comments and publish an interim rule in sufficient time to affect the 1982–83 application process.

Based on an analysis of comments received for both interim regulatory actions, the Department expects to publish one final rule which would implement both the discretionary and nondiscretionary provisions. A Spring, 1983 publication date is anticipated.

Proposed Verification

In developing this proposal the Department has sought to strike a balance between two competing concerns. First, there are abuses in the current free and reduced price application system, as documented in audits and reviews, which must be addressed through a viable income verification system. Second, States and local school officials do not have unlimited resources available to perform verification. The Department believes this draft rule will provide for a viable system without over burdening States and local officials. Moreover, States which find even the minimum requirements too onerous may request a waiver so long as they can demonstrate that an alternate system can achieve the same results.

Section 803 of Pub. L. 97–35 allows the Secretary, State agencies, and local School Food Authorities to seek verification of the information provided on applications for free and reduced price meals and free milk. The Act also requires local School Food Authorities to comply with the regulations prescribed by the Secretary concerning verification of information.

The Department believes that the possibility of verification should greatly deter under-reporting of household income of falsification of household composition. Such verification should also result in increased reporting of changes of household circumstances during the school year. For these reasons, the Department proposes to require verification of some free and reduced price applications.

Under this proposal, State agencies are required to ensure that for School Year 1982–83, at a minimum, three (3) percent or 3,000 (whichever is less) of all applications on file in each School Food Authority by October 15 are verified. State agencies have the option of using State agency staff or requiring local School Food Authorities to meet this requirement. State agencies delegating the verification responsibility to local School Food Authorities must ensure that the School Food Authorities satisfy this minimum verification requirement by January 1 of the school year. State agencies may request a waiver from FNS in regard to these verification requirements. FNS may approve the waiver if the State is able to demonstrate an alternative approach that will achieve the same results. In either case, verification may occur prior to the approval of applications;

however, the pursuit of verification shall not unduly delay the issuance of benefits to eligible children.

States which decide to meet the requirements at the State level may want to consider meeting the requirement during an AIMS review or audit or during an A–102 audit. The State may want to consider using the social security number provided on the application form to verify wages earned or other benefits through computer matching of the income reported. Should the State delegate the responsibility to the School Food Authority level, a variety of approaches become feasible. These approaches include the collection of written verification such as wage stubs, collateral contacts, and cross-program exchange of information. The Department views the verification requirement as a minimum with sufficient flexibility to allow States and local School Food Authorities to implement the requirements within existing frameworks without extensive additional financial burden.

The Department expects that most schools will opt to collect written verification of income directly from the household. This option is the most universally applicable, places the burden of responsibility on the household, and creates an awareness in the community that verification of eligibility does occur. The parent should receive clearly worded notification that the household has been selected for review and must submit the requested verification to maintain eligibility for free or reduced price benefits. The notice to parents should clearly describe the types of verification acceptable to the school, e.g. wage stubs, award letters from social security, benefit statements for unemployment compensation, court orders specifying alimony or child support, etc. Further, the notice should give the name and telephone number of the school official who can answer questions and assist the household in acquiring the necessary verification.

The initiation of collateral contacts can be used in those situations where the household is unable to acquire documentary verification. Collateral contacts can be made in person, over the phone, or by mail. The results of the contact should be written on or attached to the application noting the date, person contacted, results, and the name of the school official making the contact.

Cross-program exchange of information is another method of verification that may be utilized. State agencies and School Food Authorities should contact legal counsel to ensure that cross-program exchanges do not violate any State or Federal laws.

The Department believes an abbreviated verification procedure will suffice for food stamp households. These households undergo extensive verification in order to receive food stamp benefits. A State agency or School Food Authority may require the applicant to demonstrate current eligibility for food stamp benefits by providing "notice of eligibility" or other evidence of benefits.

An abbreviated verification procedure for food stamp households should minimize the administrative burden and cost of verification efforts since most free meal recipients are also eligible for food stamp benefits.

State agencies or local School Food Authorities would be required, under this proposal, to apply the verification efforts uniformly without regard to race, sex, color, national origin, age, or handicap. Since State and local laws differ widely, each State agency and School Food Authority should contact its legal counsel to ensure compliance with applicable laws.

Proposed Notification Requirements

The State agency or School Food Authority must terminate or reduce household benefits, if (a) the household refuses to cooperate with verification efforts, or (b) the verification effort indicates the household is ineligible to receive benefits or is eligible to receive fewer benefits. The School Food Authority must immediately notify the household in writing of a reduction or termination of benefits and allow 10 days before such termination or reduction takes place. The notice must advise the household of the change, the reasons for the change, the right to appeal the action within 10 day advance notice period and provide instructions on how to appeal. The reasons for ineligibility or reduction of benefits must be properly documented and retained on file at the School Food Authority.

Proposed Continuation of Benefits

Households which have been approved for benefits and which are subject to a reduction or termination of benefits later in the *same* school year will continue to receive benefits subject to the hearing official's decision if they appeal the adverse action within the 10 day advance notice period. Households which are denied benefits upon application shall not receive benefits pending an appeal of the decision.

Proposed Recordkeeping

State agencies will be required to maintain records demonstrating compliance with these minimum documentation and verification requirements. The Department will monitor for compliance during the management evaluation process.

List of Subjects in 7 CFR Part 245

Food Assistance Programs, Grant programs—Social programs, National School Lunch Program, School Breakfast Program, Special Milk Program, Reporting and recordkeeping requirements.

PART 245—DETERMINING ELIGIBILITY FOR FREE AND REDUCED PRICE MEALS AND FREE MILK IN SCHOOLS

Accordingly, Part 245 is proposed to be amended as follows:

1. In § 245.2, new paragraph (k) is added as follows:

§ 245.2 Definitions.

* * * * *

(k) "Verification" means substantiation of the information provided on the free or reduced price application. Verification may include but is not limited to the use of wage stubs, award letters, letters from employers, third party contacts, and computerized wage/income matching.

2. New § 245.6a is added as follows:

§ 245.6a Verification requirements.

(a) *Verification requirements.* State agencies and FNSROs, as applicable, shall ensure that for School Year 1982–83, three (3) percent or 3,000 (whichever is less) of all applications on file in each School Food Authority by October 15 are verified over the course of the school year. State agencies may request a waiver from FNS in regard to the verification requirements; *Provided,* that an alternative approach to achieve the same results is submitted in writing to and approved by FNSRO. The State agency or FNSRO, as applicable, may verify the information on the application or it may delegate the responsibility to all or selected School Food Authorities. State agencies delegating the verification responsibility to local School Food Authorities shall ensure that the School Food Authorities satisfy this minimum verification requirement by January 1 of the school year. Verification for recipients of food stamp benefits may be limited to a review to determine that the period of eligibility for food stamp benefits is current. If the food stamp certification period is found to have expired, the household shall be subject to routine verification of eligibility. Verification may occur prior to the approval of applications;

however, the pursuit of verification shall not unduly delay the issuance of benefits to eligible children. The Department encourages State agencies to verify during the first part of the school year. School officials shall, at a minimum, undertake the verification requirements prescribed by the State agency. If an applicant refuses to cooperate with the efforts to verify, eligibility shall be terminated in accordance with § 245.6a(d).

(b) *Recordkeeping.* State agencies and FNSROs, as applicable, shall maintain on file for review, a description of the verification to be accomplished during each school year. The description shall include: (1) A summary of the verification efforts including the techniques to be used; (2) the locations where verification will take place; (3) the entity responsible for verification (e.g., State agency, School Food Authority); (4) the total number of applications on file in the State by October 15 of each school year; and (5) the percentage or number of applications to be verified in the State for the current school year.

(c) *Nondiscrimination.* The verification efforts shall be applied without regard to race, sex, color, national origin, age, or handicap.

(d) *Notification.* School officials shall immediately notify families of the denial of benefits as specified in § 245.6(b). Advance notification shall be provided to families which receive a reduction or termination of benefits 10 calendar days prior to the actual reduction or termination. The notice shall advise the household of: (1) The change; (2) the reasons for the change; (3) notification of the right to appeal the action within the 10 day advance notice period; and (4) instructions on how to appeal. The reasons for ineligibility shall be properly documented and retained on file at the School Food Authority.

3. In § 245.7, paragraph (a)(ix) is amended to add the words "and that the decision of the hearing official is binding" after the word "official" and before the semi-colon.

4. In § 245.7, new paragraph (b) is added as follows:

§ 245.7 Hearing procedures for families and School Food Authorities.

* * * * *

(b) *Continuation of benefits.* When a household disagrees with an adverse action which affects its benefits and requests a fair hearing; benefits shall be continued as follows while the household awaits the hearing:

(1) Households which have been approved for benefits and which are subject to a reduction or termination of benefits later in the *same* school year, shall receive continued benefits if they appeal the adverse action within the 10 day advance notice period; and

(2) Household which are denied upon application shall not receive continued benefits.

(Sec. 803, Pub. L. 97–35, 95 Stat. 521–535 (42 U.S.C. 1758))

Signed on May 21, 1982.

John W. Bode,

Deputy Assistant Secretary for Food and Consumer Services.

[FR Doc. 82–14366 Filed 5–24–82; 8:45 am]

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AGENCY PUBLICATION ON ASSIGNED DAYS OF THE WEEK

The following agencies have agreed to publish all documents on two assigned days of the week (Monday/Thursday or Tuesday/Friday).

This is a voluntary program. (See OFR NOTICE 41 FR 32914, August 6, 1976.)

Monday	Tuesday	Wednesday	Thursday	Friday
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DOT/COAST GUARD	USDA/FNS		DOT/COAST GUARD	USDA/FNS
DOT/FAA	USDA/REA		DOT/FAA	USDA/REA
DOT/FHWA	USDA/SCS		DOT/FHWA	USDA/SCS
DOT/FRA	MSPB/OPM		DOT/FRA	MSPB/OPM
DOT/MA	LABOR		DOT/MA	LABOR
DOT/NHTSA	HHS/FDA		DOT/NHTSA	HHS/FDA
DOT/RSPA			DOT/RSPA	
DOT/SLSDC			DOT/SLSDC	
DOT/UMTA			DOT/UMTA	

Documents normally scheduled for publication on a day that will be a Federal holiday will be published the next work day following the holiday. Comments on this program are still invited.

Comments should be submitted to the Day-of-the-Week Program Coordinator, Office of the Federal Register, National Archives and Records Service, General Services Administration, Washington, D.C. 20408.

List of Public Laws

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S. 1131 / Public Law 97–177 Prompt Payment Act. (May 21, 1982; 96 Stat. 85) Price: $1.75

H.J. Res. 412 / Public Law 97–178 To authorize and request the President to designate May 20, 1982, as "Amelia Earhart Day". (May 21, 1982; 96 Stat. 89) Price: $1.75

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Tuesday, May 25, 1982

Part V

Department of Health and Human Services

Food and Drug Administration

Over-the-Counter Oral Health Care and Discomfort Drugs; Establishment of a Monograph

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 354

[Docket No. 80N-0228]

Drug Products for the Relief of Oral Discomfort for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration.

ACTION: Advance notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing an advance notice of proposed rulemaking that would establish conditions under which over-the-counter (OTC) drug products for the relief of oral discomfort (drugs which relieve oral discomfort when applied topically to teeth and gums) are generally recognized as safe and effective and not misbranded. This notice is based on the recommendations of the Advisory Review panel on OTC Dentifrice and Dental Care Drug Products and is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments by August 23, 1982 and reply comments by September 22, 1982.

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

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

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on July 13, 1978 a report on OTC drug products for the relief of oral discomfort from the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products. This report is one of three issued by this Panel. Other reports by this Panel concerned oral mucosal injury drug products (published in the **Federal Register** of November 2, 1979 (44 FR 63270)) and anticaries drug products (published in the **Federal Register** of March 28, 1980 (45 FR 20666)). FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed rule containing (1) the monograph recommended by the Panel, which establishes conditions under which OTC drug products for the relief of oral discomfort are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs' not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC drug products for the relief of oral discomfort as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule. Final agency action occurs in the final monograph, which has the status of a final rule.

The agency's position on OTC drug products for the relief of oral discomfort will be stated initially when the tentative final monograph is published in the **Federal Register** as a proposed regulation. In the preamble to the tentative final monograph, the agency also will announce its initial determination whether the monograph is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the tentative final monograph is published. At that time FDA also will consider whether the monograph has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC drug products for the relief of oral discomfort. Types of impact, may include, but are not limited to, the following: increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC drug products for the relief of oral discomfort should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC drug products for the relief of oral discomfort submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after June 24, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III durgs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process, before the establishment of a final monograph.

Although it was not required to do so under *Cutler*, FDA will no longer use the terms "Category I," "Category II," and "Category III" at the final monograph stage in favor of the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III because that was the framework in which the Panel conducted its evaluation of the data.

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 6 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, on OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions which 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. Further, any OTC drug products subject to this monograph which are 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.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in dentifrice and dental care drug products, except mouthwashes and oral antiseptics, was issued in the **Federal Register** of January 30, 1973 (38 FR 2781). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' ")

Under § 33.10(a) (1) and (5), the Commissioner appointed the following Panel to review the data and information submitted and to prepare a report on the safety, effectiveness, and labeling of those products:

Louis P. Gangarosa, D.D.S., Ph. D., Chairman
Joseph J. Aleo, D.D.S., Ph. D. (appointed September 1, 1973)
Howard H. Chauncey, D.M.D., Ph. D. (resigned April 30, 1976)
Valerie Hurst, Ph. D.
Joy B. Plein, Ph. D.
Delos E. Raymond, D.D.S.
Roger H. Scholle, D.D.S., M.S.
Lawrence E. VanKirk, Jr., D.D.S., M.P.H. (appointed June 29, 1976)
Benjamin O. Watkins D.D.S. (resigned August 1, 1973)

Nonvoting liaison members served on the Panel as follows: Judy Jackson, Esq., nominated by the Consumer Federation of America, served as the consumer liaison until April 1974 followed by Mary Plaska, nominated by the American Public Health Association, until May 1976 followed by Sandra Zimmerman, nominated by the Consumer Federation of America. Lester D. Apperson, Ph. D., nominated by the Cosmetic, Toiletry, and Fragrance Association, served as an industry liaison. Joseph L. Kanig, Ph. D., nominated by the Proprietary Assocation, also served as an industry liaison until January 1978.

The following FDA employee assisted the Panel: Clarence C. Gilkes, D.D.S., served as Executive Secretary. Michael D. Kennedy served as Panel Administrator until January 1978 followed by Thomas D. DeCillis, R. Ph. Melvin Lessing, M.S., R. Ph. served as Drug Information Analyst until June 1977. George Kerner, M.S., served as Consumer Safety Officer. Cindy Barkdull served as special assistant from July 1977 to April 1978. Elmer M. Plein, Ph. D., and Gordon H. Schrotenboer, Ph. D., served as consultants to the Panel.

The Panel was first convened on April 24, 1973, in an organizational meeting. Working meetings were held on May 24 and 25, June 21 and 22, August 15 and 16, October 10 and 11, November 29 and 30, 1973; January 17 and 18, February 27 and 28, April 3 and 4, May 9 and 10, June 19 and 20, July 24 and 25, September 19 and 20, October 16 and 17, December 4 and 5, 1974; January 15 and 16, February 26 and 27, April 2 and 3, May 7 and 8, June 24 and 25, August 12, 13, and 14, October 9 and 10, December 3 and 4, 1975; January 23 and 24, February 24 and 25, March 31 and April 1, May 11 and 12, June 30 and July 1, July 28 and 29, August 25, and 26, October 5 and 6, December 1 and 2, 1976; January 12 and 13, March 9 and 10, April 20 and 21, June 1 and 2, July 13 and 14, August 24 and 25, October 19 and 20, November 30 and December 1, 1977. January 17 and 18, March 11 and 12, April 26, 27, and 28, May 30 and 31, and June 1, and July 11, 12, and 13, 1978.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration (address above).

The following individuals were given on opportunity to appear before the Panel to express their views either at their own or at the Panels' request on all issues before the Panel:

John E Alman, M.A.
Hazen J. Baron, D.D.S., Ph. D.
I. B. Bender, D.D.S.
Robert Blank, Ph. D.
Malcolm Boone, D.D.S.
R. K. Boutwell, Ph. D.
Herbert Brilliant, D.D.S.
Richard C. Brogle, Ph. D.
Finn Brudevold, D.D.S.
Lewis P. Cancro, Ph. D.
A. Chasens, D.D.S.
Neal W. Chilton, D.D.S.
Stephen A . Cooper , D.M.D., Ph. D.
D. Walter Cohen, D.D.S.
William E. Cooley, Ph.D.
Robert Ellison, D.D.S., M.S.
H. Fogels, D.D.S.
Sol Gershon, Ph. D.
William Gold, Ph. D.
Hary Gordon, Ph. D.
Hans Graf, D.D.S.
F. Healy, Ph. D.
John Hefferren, Ph. D.
L. Kenneth Hiller, Ph. D.
George F. Hoffnagle, Sc. D.
Herschel S. Horowitz, D.D.S., M.P.H.
Homer Jamison, D.D.S., Ph. D.
Marvin Kamisky, Ph. D.
Krishan Kapur, D.M.D., M. Sc.
Kenneth Kasses, Ph. D.
Phillip B. Lawson
Edgar Lazo-Wasem, Ph. D.
Donald A. M. MacKay, Ph. D.
John H. Manhold D.M.D.
Craig R. Means, D.D.S., M. Sc.
Murray Rosenthal, M.S.
Albert L. Russell, D.D.S., M. Ph.
Bernard Schneider, D.D.S.
James H. Stanton
Willard J. Tarbet, D.D.S., Ph. D.
Patrick Toto, D.D.S.
Leonard Townes, D.D.S.
Aaron Trubman, D.D.S.
Paul Vinton, D.D.S.
Carrol S. Weil, M.A.
Elizabeth K. Weisburger, Ph. D.
S. C. Yankell, D.D.S.
K. Yeh, Ph. D.
A. Albert Yurkstas, D.M.D.

No person who so requested was denied an opportunity to appear before the Panel.

The Panel was charged to review submitted data and information for OTC dentifrice and dental care drug products.

Because all such agents are not used for the same purpose, it was not possible for the Panel to establish a single standard of requirements for effectiveness of each product. Therefore, in an attempt to simplify categorization of ingredients and labeling claims, the Panel placed the dental care drug products into the following therapeutic classifications: (1) Agents for oral mucosal injury, (2) agents for the relief of oral discomfort, (3) anticaries agents, (4) dental plaque disclosing agents, and (5) denture aids.

On May 28, 1976, the Medical Device Amendments of 1976 became law. This legislation amends the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 301 et seq.) and provides new authority to assure the safety and effectiveness of medical devices. Several products previously regulated as drugs that were under review by the Panel came within the definition of a medical device under these amendments. The FDA reviewed the products previously regarded as drugs and concluded that the following products as published in the **Federal Register** of December 16, 1977 (42 FR 63472) fall within the definition of a medical device: denture cushions, dental adhesives, dental reliners and repair kits, denture cleansers, and plaque-disclosing kits. The Panel wishes to point out that during its deliberations "kits" were not specifically addressed and that the Panel's terminology for dental devices differs from that published in the **Federal Register.** The Panel used the following terminology in evaluating these products: denture adhesives, denture reliners, denture repair products, denture cleansers, and dental plaque-disclosing agents.

In a notice published in the **Federal Register** of May 2, 1978 (43 FR 18769), FDA announced that it had transferred the responsibility for regulating OTC dental care devices from the agency's Bureau of Drugs to its Bureau of Medical Devices (BMD). In addition, the notice announced that the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products had summarized its findings and recommended that the agency transfer that portion of its report concerning products now regulated as medical devices, together with the data and information submitted in response to the January 30, 1973 notice, to BMD. A summary of the Panel's conclusions concerning the safety, effectiveness, and labeling of those products is included in the Panel's minutes for the March 11 and 12, 1978 meeting.

The Panel presents its conclusions and recommendations for drug products for the relief of oral discomfort in this document. The Panel's conclusions and recommendations for oral mucosal injury drug products were published in the **Federal Register** of November 2, 1979 (44 FR 63270) and the Panel's conclusions and recommendations for anticaries drug products were published in the **Federal Register** of March 28, 1980 (45 FR 20666).

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through July 13, 1978, in arriving at its conclusions and recommendations.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel's findings with respect to OTC drug products for the relief of oral discomfort are set out in three categories:

Category I. Conditions under which OTC drug products for the relief of oral discomfort are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC drug products for the relief of oral discomfort are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insufficient to permit final classification at this time.

The Panel reviewed 25 ingredients for relief of oral discomfort. The Panel placed one ingredient in Category I, three ingredients in Category II, and nine ingredients in Category III for use as agents for the relief of toothache. The Panel placed three ingredients in Category I, two ingredients in Category II, and three ingredients in Category III for use as oral mucosal analgesics. The Panel placed one ingredient in Category I, no ingredients in Category II, and one ingredient in Category III for use as oral mucosal protectants. The Panel placed no ingredients in Category I, one ingredient in Category II, and five ingredients in Category III for use as tooth desensitizers. (The number of ingredient classifications does not equal the number of ingredients reviewed because some ingredients were reviewed for more than one labeled use.)

I. Submission of Data and Information

Pursuant to the notice published in the **Federal Register** of January 30, 1973 (38 FR 2781) requesting the submission of data and information on OTC dentifrice and dental care drug products, the following firms made submissions relating to the indicated products that, the Panel has further determined, contain active ingredients or labeling which may be appropriately classified as drug products for the relief of oral discomfort.

A. Submissions by Firms

Firms and Marketed Products

Abbott Laboratories, North Chicago, IL 60064, Butyn Metaphen Dental Ointment.

A-Trol Laboratories, Topeka, KA 66604, I.D. Denture Medication.

Block Drug Co., Jersey City, NJ 07302, Jiffy Toothache Drops, Poloris Poultices, Sensodyne.

Commerce Drug Co., Inc. Farmingdale, NY 11735, Ora-Jel, Baby Ora-Jel, Ora-Jel D.

C. S. Dent & Co., Cincinnati, OH 45202, Dent's Toothache Drops, Dent's Toothache Gum, Dent's Lotion-jel, Dent's Dental Poultice.

Denver Chemical Manufacturing Co., Stamford, CT 06904, Dr. Hand's Teething Gel, Dr. Hand's Teething Lotion, Pain-A-Lay.

Eaton Laboratories, Norwich, NY 13815. Chloraseptic Mouthwash and Gargle.

Eneglotaria Medicine Co., Inc., Santurce, PR 00907, Gotas Dentil, Erpen.

John Arthur Geyer Co., Bedford, NH 03102, Kank-A.

International Pharmaceutical Corp., Warrington, PA 18976, DeSense Dental Gel, Protect Dental Gel.

K. I. K. Co., Bethlehem, PA 18016, Cheramist #30.

Lorvic Corp., Saint Louis, MO 63134, Desensitizer.

McKesson Laboratories, Fairfield, CT 06430, OraFix Medicated.

Pfizer, Inc., New York, NY 10017, Thermodent Toothpaste.

Red Cross Chemical Works, Inc., Chicago, IL 60647, Toothache Outfit.

Rilox Co., Inc., New Orleans, LA 70122, Creole Toothache Wax.

Rystan Co., Inc., White Plains, NY 10605, Chloresium Toothpaste, Chloresium Dental Ointment, Chloresium Solution.

Sanlor Laboratories, Washington, DC 20006, Endoflas, F.S.

Vick Chemical Co., New York, NY 10017, Benzodent Analgesic Denture Ointment.

Whitehall Laboratories, Inc., New York, NY 10017, Anbesol.

Zelite Corp., New York, NY 10017, Dent-Zelite Toothache Remedy.

In addition, the following firms made related submissions:

Abbott Laboratories, North Chicago, IL 60064, Butyn Metaphen Dental Ointment (Additional data).

Block Drug Co., Jersey City, NJ 07302, Sensodyne, Poloris Dental Poultice (Additional data).

Commerce Drug Co., Inc., Farmingdale, NY 11735, Baby Ora-Jel (Additional data).

Eaton Laboratories, Norwich, NY 13815, Chloraseptic Mouthwash and Gargle (Additional data).

International Pharmaceutical Corp., Warrington, PA 18976, Protect Dental Gel (Additional data).

Rystan Co., Inc., White Plains, NY 10605, Chloresium Toothpaste, Chloresium Dental Ointment, Chloresium Solution (Additional data).

Sanlor Laboratories, Washington, DC 20006, Endoflas, F.S. (Additional data).
Vick Chemical Co., New York, NY 10017, Vicks Potassium Nitrate Toothpaste, Testing Method.
Whitehall Laboratories, Inc., New York, NY 10017, Anbesol (Additional data).

B. Ingredients Submitted to the Panel

1. *Labeled ingredients contained in marketed products submitted to the Panel.*

Alcohol
Beeswax
Benzocaine
Benzoin compound tincture
Benzyl alcohol
Boric acid
Butacaine
Calcium carbonate
Camphor
Capsicum oleoresin (capsicum)
Carbolic acid (phenol)
Cellulose gum
Chloroform
Citric acid
Clove oil
Creosote
Cresol
D & C Red Color 11251
Distilled water
Edetate disodium (EDTA)
Eugenol
Fluidextract myrrh
Formaldehyde
Glycerin
Hamamelis water
Hops
Hydroxyquinoline sulfate
Iodine
Magnesium aluminum silicate
Menthol
Methylparaben
Methyl salicylate
Nitrogen, compressed (propellant)
Nitromersol chloride
Oil of cassia
Oil of cloves
Oxyquinoline
Paraffin wax (paraffine)
Pellitory tincture
Petrolatum
Phenol
Pluronic F–127™ gel
Potassium nitrate
Potassium sulfate
Propylene glycol
Propylparaben
Sandarac
Sassafras root
Silica
Sodium bicarbonate
Sodium borate
Sodium chloride
Sodium citrate
Sodium fluoride
Sodium lauryl sulfate
Soduim phenolate
Sodium saccharin
Sodium sulfate
Sorbitol
Stannous fluoride
Strontium chloride
Thymol
Thymol iodide
Water

2. *Other ingredient reviewed by the Panel in addition to the submitted data.*

Sodium monofluorophosphate

C. Classification of Ingredients

1. *Active ingredients.*

Benzocaine
Benzoin preparations (benzoin tincture and compound benzoin tincture)
Benzyl alcohol
Butacaine sulfate (butacaine)
Camphor
Capsicum (capsicum oleoresin)
Citric acid
Clove oil (oil of cloves)
Creosote
Cresol
Eugenol
Formaldehyde solution (formaldehyde)
Menthol
Methyl salicylate
Myrrh, fluidextract (fluidextract myrrh)
Phenol (carbolic acid)
Phenolate sodium (sodium phenolate)
Potassium nitrate
Sodium citrate
Sodium fluoride
Sodium monofluorophosphate
Stannous fluoride
Strontium chloride
Thymol
Thymol iodide

2. *Inactive ingredients.*

Beeswax
Calcium carbonate
Cellulose gum
Chloroform
Cinnamon oil (cassia oil, oil of cassia)
D & C red color 11251
Distilled water
Edetate disodium (EDTA)
Glycerin
Hops
Magnesium aluminum silicate
Nitrogen, compressed (propellant)
Paraffin wax (paraffine)
Petrolatum
Poloxamer 407 (Pluronic F–127™ gel)
Potassium sulfate
Propylene glycol
Propylparaben
Sandarac
Sassafras root
Silica
Sodium Bicarbonate
Sodium chloride
Sodium lauryl sulfate
Sodium saccharin
Sodium sulfate
Sorbitol
Water

3. *Ingredients deferred to the Advisory Review Panel on OTC Oral Cavity Drug Products.*

Alcohol (antiseptic)
Alum (astringent)
Boric acid (astringent)
Camphor (antimicrobial)
Iodine (antiseptic)
Hamamelis water (astringent)
Hydroxyquinoline sulfate (antiseptic)
Menthol (antiseptic)
Methylparaben (preservative)
Methyl salicylate (antiseptic)
Nitromersol chloride (antiseptic)
Oxyquinoline (antiseptic)
Pellitory tincture (astringent)
Phenol (antiseptic)
Propylparaben (antiseptic)
Sodium borate (antiseptic)

4. *Ingredients deferred to the Advisory Review Panel on OTC Miscellaneous External Drug Products.*

Camphor (cold sore claim)
Benzoin preparations (benzoin tincture and compound benzoin tincture) (Herpes simplex claims).

5. *Ingredients deferred to the Bureau of Medical Devices.*

Paraffin wax (paraffine) (as a denture cushion)

6. *Indications deferred to the Advisory Review Panel on OTC Oral Cavity Drug Products.*

All antiseptic claims:
"For rapid and effective relief of minor sore throat."
"For fast temporary relief of minor throat and mouth soreness."
"For rapid relief of minor throat and mouth soreness."

7. *Indications deferred to the Advisory Review Panel on OTC Miscellaneous External Drug Products.*

All cold sore and fever blister (Herpes simplex) claims.

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of April 26, 1973 (38 FR 10306). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after June 24, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Definitions

The following definitions have been adopted by the Panel. These definitions reflect the Panel's intended meaning of terms as specifically used in this document in reference to drug products for the relief of oral discomfort. Some of these definitions also apply to the other drug categories reviewed by the Panel. Some degree of variation with other definitions of the same terms may exist.

1. *Agent for the relief of oral discomfort.* An agent which, when applied topically, has direct or indirect capability to relieve oral discomfort. This category of drugs includes oral mucosal analgesics, tooth desensitizers, oral mucosal protectants, and agents for the relief of toothache.

2. *Agent for the relief of toothache.* An ingredient used for the temporary relief of pain arising as a result of an open tooth cavity.

3. *Anesthetic.* A drug which causes reversible loss of feeling or sensation. Anesthetics are of two types. A "general" anesthetic is given by inhalation or by intravenous injection, and the agent causes loss of consciousness as well as loss of sensation. A "local" anesthetic is applied to the nerve tissue, in which it blocks sensory receptors and passage of nerve impulses. In a professional practice, the dentist administers local anesthetics by (1) injection into the area adjacent to the nerve(s) to be blocked, or (2) application of the agent (a "topical" or "surface anesthetic) to the oral mucosa. The term "oral mucosal analgesic" is used synonymously with "topical" or "surface anesthetic" or "topical analgesic."

4. *Analgesic (topical).* An ingredient used in drug products for surface application to provide temporary relief of discomfort by an anesthetic or analgesic effect.

5. *Anodyne.* "Anodyne" is synonymous with "topical analgesic." (See part II. paragraph A.4. above—Analgesic (topical).)

6. *Antiseptic.* A preparation which contains chemicals intended to kill or temporarily prevent multiplication of harmful germs which may be present on the skin or oral mucous membranes.

7. *Bioavailability.* The degree to which the drug is absorbed from a dosage form into the body or to its site of action.

8. *Buffering agent.* An agent or system which has the ability to resist a change in pH (hydrogen ion concentration), particularly in aqueous solution, upon the addition of an acid, alkali, or upon dilution with a solvent.

9. *Carcinogenic.* Producing cancer. Carcinogenic agents may be broadly categorized as (a) chemical, (b) physical, (c) viral, or (d) hormonal. Not all species are susceptible to every known carcinogen; it is common to find that a carcinogen which is active in one species will be inactive in another.

10. *Cementum.* The bonelike material covering the root of the tooth. Cementum contains about 45 to 50 percent organic and the balance, inorganic matter. It contains a great number of fibers which attach the tooth to the bone.

11. *Counterirritant.* An irritating drug that is applied locally to the skin or oral mucosa for relief of pain originating from a structure other than the site of application. For example, an irritant drug might be applied in a dental poultice to the oral mucosa surrounding a tooth with a painful pulpitis.

12. *Demulcent.* A protective agent which is employed primarily to alleviate irritation, particularly of mucous membranes or abraded tissues. It is also often applied to the skin.

13. *Dental calculus.* Mineralized dental plaque accumulates on the tooth surface principally at the gingival margin. One of the major fates of plaque is mineralization. Plaque serves as a matrix for calculus formation. The surface of calculus is usually covered with a nonmineralized layer of plaque. The main irritating feature of calculus is its surface plaque rather than its calcified surface or interior.

14. *Dental care agent.* Any drug or dosage form used to treat or prevent disease of the teeth or soft tissue in the oral cavity.

15. *Dental (dentin) hypersensitivity.* A term which implies that the teeth are much more reactive than normal to sensory stimuli such as heat, cold, sour, sweet, or touch. Hypersensitivity can occur when dentin is exposed to the oral environment as a result of gingival recession, abrasion, erosion, or a defect in the enamel or cementum.

16. *Dental poultice.* A topical dosage form which is confined within a porous sac and is applied to the oral mucous membrane in order to supply medication in the presence of heat and moisture.

17. *Dental rinse.* A term used to designate a liquid dosage form for rinsing between and around the teeth.

18. *Dentifrice.* In this document a dentifrice is a substance used with a toothbrush to clean the accessible surfaces of the teeth. Dentifrices are ordinarily composed of water, detergent, humectant, binder, flavoring agents, and a finely powdered abrasive as the principal ingredient. In this document a dentifrice is considered to be an abrasive-containing dosage form for delivering therapeutic agents to the teeth.

19. *Dentin.* Dentin is the calcified tissue forming the bulk of a tooth. It is composed of approximately 70 percent inorganic material, 18 percent organic material, and 12 percent water. Dentin is covered by the enamel of the tooth crown and the cementum of the root. It encloses the soft pulpal tissues of the tooth. Dentin has a tubular structure, and processes from cells in the pulp (odontoblasts) penetrate the dentinal tubules. There are three types of dentin—primary dentin, secondary dentin, and tertiary dentin.

a. *Dentin, primary.* The primary dentin is the well-structured dentin that is deposited during the original formation of a tooth. Dentin deposited later in life differs in structure and can be distinguished from primary dentin microscopically by a demarcation line that stains darkly.

b. *Dentin, secondary (reparative, irritation, adventitious, or tertiary dentin).* Dentin formed after the original primary dentin of the tooth has been deposited is termed "secondary dentin." It forms on the inner, or pulpal, surface of the primary dentin as a physiologic process or as a pathologic response to thermal, mechanical, or chemical irritants. The secondary dentin is not as well-structured as primary dentin and can be distinguished microscopically by its irregular morphologic pattern.

c. *Dentin, tertiary.* Although all dentin that is not primary dentin has traditionally been considered to be secondary dentin, some dental scientists now distinguish between secondary and tertiary dentin. The term "tertiary dentin" is used to designate dentin forming as the result of more severe injuries or insults to a tooth, such as dental caries, marked abrasion, or extensive erosion. The tertiary dentin is of very poor tubular structure and is limited to the area of irritation. In this context, secondary dentin differs from tertiary dentin in that secondary dentin forms as the result of mild biologic effects and is of a more generalized deposition.

In this document, evaluation of the active ingredients is not related to any specific type of dentin.

20. *Dentin desensitizer.* A drug which acts on the dentin to block perception of those stimuli which are usually not perceived by normal subjects but which are perceived by patients with dental hypersensitivity.

21. *Dentinal tubule.* Microscopic channels in the dentin which contain (a) the odontoblastic process (projection of the dentin-producing cells which line the pulp chamber and produce dentin), (b) tissue fluid bathing the process, and (c) varying degrees of mineral. It is controversial whether these tubules contain nerves, but there is general agreement that the tubules contain the means for transmitting pain perception.

22. *Dosage.* A schedule that includes the amount of drug that is ingested or applied at one time (the dose) and the time intervals at which the dose is given;

the schedule may include the duration of therapy.

23. *Dosage form.* The pharmaceutical preparation, e.g., solution, suspension, paste, tablet, ointment, in which the drug is administered.

24. *Dose.* The quantity of a drug that is ingested or applied at one time.

25. *Dose-response.* The relationship between the dose of a drug and the magnitude of the effect produced by that dose.

26. *Double-blind study.* A testing procedure in which neither the investigator nor the subject (patient) knows whether an experimental drug or its control has been administered.

27. *Enamel.* The compact and hard substance that covers the crown of the tooth and provides protection for the dentin. The inorganic content of mature enamel amounts to 96 to 97 percent, by weight, the remainder consisting of organic matter and water.

28. *Fluoride.* The term "fluoride" is used to denote the inorganic forms in which fluorine has combined with other elements. The term "fluoride ion" denotes the negatively charged atom of the chemical element fluorine. The deposition of fluoride in dental enamel has been shown to increase resistance to enamel solubility and, therefore, dental decay.

29. *Gingivitis.* Inflammation occurring in the marginal or papillary gingiva as a response to bacterial plaque.

30. *Hypersensitivity.* Literally means, "more sensitive than normal." In general health care, the term is almost synonymous with allergy and implies that the person has been exposed to a drug, develops antibodies to it, and then reacts adversely to the drug upon subsequent exposure, whereas the normal subject does not. (See part II. paragraph A.15 above—Dental (dentin) hypersensitivity.)

31. *Immediate dentures.* A denture is a dental prosthesis made to replace lost natural teeth in a dental arch. A partial denture replaces a few teeth; a full denture replaces all the lost teeth in an arch (upper or lower). An immediate denture is one that is fabricated prior to the extraction of a few natural teeth and placed in the mouth immediately following the extraction of the natural teeth as part of the surgical procedure.

32. *Minor gum disorders (injury).* Inflammation related to mechanical irritation or minor injury of the gingival tissues. The Panel does not consider gingivitis caused by dental plaque to be a minor gum disorder amenable to self-diagnosis or treatment by OTC preparations.

33. *Mouthwash (oral rinse).* A solution often containing breath-sweetening, astringent, demulcent, detergent, or germicidal agents which is used for freshening and cleansing the mouth, or for gargling. In some instances, such a vehicle may be used to deliver an active drug to the oral mucosa or teeth. The Panel prefers the terms "oral rinse" and "dental rinse" according to their respective areas of use (for the oral mucosa or the teeth) rather than "mouthwash."

34. *Necrosis.* Refers to circumscribed localized areas of cell or tissue death caused by almost any type of severe injury.

35. *Obtundent.* "Obtundent" is used synonymously with "topical analgesic." (See Part II. paragraph A.4 above—Analgesic (topical).)

36. *Oral mucosal analgesic.* An ingredient used in dental care drug products for topical application in the oral cavity to provide temporary relief of oral discomfort by an anesthetic or analgesic effect.

37. *Oral mucosal injury agent.* An agent which relieves oral soft tissue injury, e.g., by cleansing or promoting the healing or oral wounds (minor oral irritations).

38. *Oral mucosal protectant.* An agent which is a pharmacologically inert substance which forms an adherent, continuous, flexible, or semirigid coating when applied to the oral mucous membranes. The coating protects the irritated area from further irritation due to the activity of oral structures.

39. *Pharmacotherapeutic.* The Panel has classified ingredients into various pharmacotherapeutic groups according to the expected therapeutic effect at the intended site of action.

40. *Placebo.* An inactive substance or preparation used in controlled studies to determine the effectiveness of an agent presumed to be active. Generally, a placebo preparation will be identical to the test preparation except that the active or test ingredient will not be present.

41. *Professional labeling.* Drug usage directions for the use of a product intended for, and distributed only to, health care professionals.

42. *Prophylactic.* The term "prophylactic" indicates the prevention of disease. In this document, "prophylactic" is synonymous with "preventative."

43. *Sloughing.* A slough is a mass of dead tissue in, or cast out from, living tissue. Sloughing is the formation or separation of dead from living tissue.

44. *Systemic effect.* An effect related to the entire body as contrasted to a local effect which is an effect on one specific structure. In general, drugs which are absorbed into the blood stream can be assumed to exert systemic effects, although the desired and the observable sites of action may be fairly specific structures or organs.

45. *Teratogenicity.* The capacity of a drug to exert a harmful effect on a developing fetus. Agents which are suspected or known teratogens should not be taken during actual or suspected pregnancy.

46. *Tooth desensitizer.* "Tooth desensitizer" is synomymous with "dentin desensitizer." (See part II. paragraph A.20. above—Dentin desensitizer.)

47. *Topical analgesic (topical anesthetic).* In this report, "topical anesthetic" is used synonymously with "topical analgesic." See part II. paragraph A.4. above—Analgesic (topical).

B. General Comments

The Panel recognizes that there is a consumer population which has an occasional need for OTC preparations to treat minor trauma or irritation which casuses inflammation of a transient nature to the gums or teeth. The Panel has classified such preparations as drug products for the relief of oral discomfort. The drugs within this classification have been subclassified into the following pharmacotherapeutic groups: (1) Agents for the relief of toothache, (2) oral mucosal analgesics, (3) oral mucosal protectants, and (4) tooth desensitizers. In addition, the Panel will discuss dental poultices as a dosage form.

1. *Agents for the relief of toothache.* Agents for the relief of toothache provide temporary relief of pain arising as a result of an open tooth cavity. A counterirritant may also be an agent for the relief of toothache. All agents for the relief of toothache except counterirritants are applied into an open tooth cavity. Counterirritants are applied in a dental poultice to the gingiva surrounding a tooth with a painful pulpitis. Agents for the relief of toothache have been on the market for a long period of time; they probably had their origin in empiric medicine.

The dental profession has voiced considerable concern about the safety and effectivenes of agents for the relief of toothache (Ref. 1). The Panel reviewed complaints about various dental products from a variety of sources. In brief, many dentists and dental organizations expressed concern that agents for the relief of toothache can have harmful effects and that their effectiveness is doubtful (Refs. 1 and 2).

After studying consultants' reviews and comments, and after reviewing the submissions and other pertinent

literature, the Panel came to the conclusion that because there may be a significant target population who could obtain temporary relief from some toothache medications, it would be helpful to have such medications, it would be helpful to have such medication available to the consumer.

2. *Oral mucosal analgesics.* Oral mucosal analgesics are surface or topical application to provide temporary relief of oral discomfort. Some injectable local anesthetics have surface anesthetic properties when applied in ointment, gel, or other topical dosage form. The most commonly used surface anesthetics for OTC dental use are benzocaine and butacaine. Benzocaine (ethylaminobenzoate) is very commonly used as a surface anesthetic; slow absorption makes it safe for use on wounds and mucous membranes (Ref. 3). Various aromatic principles and alcohols also have modest to intense surface anesthetic effects. Tainter (Ref. 4) found that phenol, benzyl alcohol, menthol, and chlorobutanol have topical anesthetic activity.

3. *Oral mucosal protectants.* Oral mucosal protectants are insoluble, pharmacologically inert substances that form adherent, continuous, flexible, or semirigid coats when applied to the oral mucous membranes (Ref. 5). These coatings help to protect the irritated areas of the mouth from further irritation from chewing, swallowing, and other mouth activity. When applied locally to the oral mucous membranes, they can provide temporary relief of discomfort of minor thermal or chemical burns, irritations, or ulcerations resulting from mechanical trauma and aphthous ulcerations (canker sores).

4. *Tooth desensitizers.* Tooth desensitizers are agents used to treat "hypersensitive" (ultrasensitive) dentin. This condition can develop when dentin is exposed to the environment of the oral cavity. The dentin, which contains the sensory apparatus of the tooth, is normally covered by either enamel (crown) or cementum (root). When the latter calcified structures are absent as a result of erosion, abrasion, removal by the dentist, a defect in the tooth, or some other cause, the resultant exposed dentin can become ultrasensitive to various stimuli. Temperature change, mechanical stimuli, and certain chemicals may then induce a painful response. The dentist may make the diagnosis of hypersensitive dentin if all carious lesions have received professional treatment, if there are no restorations causing the ultransensitive response, and if there are no symptoms suggestive of pulpal pathology. Even though the consumer cannot make this diagnosis without professional advice, it is still considered useful by the Panel to have tooth desensitizers available OTC for temporary use until a dentist can be seen or after a dentist has made a diagnosis of dental hypersensitivity and recommends the use of a tooth desensitizer. It is estimated that there is a significant target population with hypersensitive dentin which would use an OTC dentifrice for desensitization (Ref. 6). Therefore, the Panel recommends that these products be made available to the public with a warning that, unless recommended by a dentist, the products are to be used for not more than 2 weeks. The labeling should include appropriate statements on the dangers of neglecting dental care. (See part II. paragraph C.4. below—Warnings).

5. *Dental poultices.* Dental poultices are topical dosage forms containing medication enclosed within a porous sack. When applied to the oral mucous membrane in the presence of moisture, the dental poultice releases the active ingredient.

Dental poultices are in many respects similar to externally applied cataplasms or poultices, one of the oldest classes of pharmaceutical preparations. These products are defined as being usually soft, mushy, or semiliquid preparations to be applied to the skin for the purpose of either stimulating a body surface or alleviating an inflamed area by supplying medicaments in the presence of moisture (Ref. 7). Poultices are reported to be applied for the purpose of drawing infectious materials from diseased tissues as a result of the absorptive qualities of the ingredients used (Ref. 8).

The Panel believes that there is a possibility of a dental poultice becoming accidentally lodged in the throat or in the respiratory tract if the user falls asleep with the poultice in place. The Panel recommends, therefore, that the label of the products carry the warning, "To avoid danger of choking do not leave a poultice in the mouth during periods of sleep."

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C. Labeling for OTC Drug Products for the Relief of Oral Discomfort

The Panel reviewed and concurs with the FDA's OTC drug labeling regulations (21 CFR 201.61 (a), (b), and (c) and 21 CFR 330.10(a)(4)(v)). Having reviewed all of the submitted labels of OTC drug products for the relief of oral discomfort, the Panel recommends that labeling include the following:

1. *Ingredients.* Dentifrice and dental care agents should contain only active ingredients plus such inactive ingredients as may be necessary for formulation. The label should state the name and quantity of each active ingredient in appropriate units to be specified later in each section of this document. The Panel encourages the use of metric units when possible.

The labeling must indicate the principal intended action of the active ingredient as well as the indication for use of the product. The Panel considers that the labeling for any product that contains an active ingredient for which no claim is made is misleading.

For various reasons, individuals may wish to avoid using certain inactive ingredients found in drug products. Such reasons include allergic reactions, previous idiosyncratic responses, safety concerns (whether valid or not), or personal preference. It is impossible to make a free choice in this regard unless all the components of drug products are listed on the labels. Therefore, this Panel strongly recommends that all inactive ingredients be listed on the label in descending order of quantity. However, the product should not imply or claim that its inactive ingredients have a therapeutic benefit.

The Panel recognizes that although full disclosure of flavoring and coloring ingredients is desirable, this may be impractical and confusing because of the large number of ingredients which may be involved. Thus, flavoring and coloring ingredients may be listed in accordance with present regulations for

labeling such ingredients in cosmetic products (21 CFR 701.3).

2. *Indications.* The indications for use of an oral mucosal protectant, tooth desensitizer, oral mucosal analgesic, or agent for the relief of toothache should be simply and clearly stated and should provide the user with a reasonable expectation of results to be anticipated from use of the product.

Statements of indications for use should be specific and confined to the conditions for which the product is recommended. No reference should be made, or implied, regarding the alleviation or relief of symptoms unrelated to the condition accepted as an indication for use of the product. Thus, a prominent and conspicuous statement must be made of general pharmacotherapeutic action. For example, drug products for the relief of oral discomfort should be labeled to indicate their usage, i.e., "agent for the relief of toothache," "oral mucosal protectant," "oral mucosal analgesic," etc.

The Panel concludes that drug products which have antiplaque, plaque control, or gingivitis claims are not currently appropriate for the OTC market because there is no general recognition of any such drug products as safe and effective for these indications at this time. Accordingly, the Panel recommends that such drug products and claims should be evaluated by FDA through the new drug application (NDA) procedure.

3. *Directions for use.* The directions for use should be clear, direct, and provide the user with sufficient information to permit safe and effective use of the product.

The label should include a clear statement of the usually effective minimum and, where applicable, maximum dose (or concentration if more appropriate) per time interval. If dosage varies with the consumer's age, the directions should be broken down by age groups. In appropriate instances, the usual directions may be followed by a statement recommending the supervision of a dentist or physician in the use of the product. The Panel will recommend specific directions for use under each drug statement in later sections of this document.

4. *Warnings.* Labeling of dental care products should include warnings against unsafe use, side effects, and adverse reactions. The Panel considers the following warnings necessary for the safe use of OTC drug products for the relief of oral discomfort.

a. *For all OTC drug products for the relief of oral discomfort.* (1) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(2) "Do not swallow."

(3) "Do not exceed recommended dosage."

b. *For all drug products for the relief of oral discomfort except for products containing tooth desensitizer active ingredients.*

"Not to be used for a period exceeding 7 days."

c. *For all drug products for the relief of oral discomfort except for products containing butacaine sulfate.*

"Children under 12 years of age should be supervised in the use of this product."

d. *For all drug products for the relief of oral discomfort containing butacaine sulfate.* (1) "Do not use in children under 12 years of age unless recommended by a dentist or physician."

(2) "Do not use more than one unit at a time."

(3) "Do not repeat except after 3 hours."

(4) "Do not exceed three doses daily."

e. *For all drug products for the relief of oral discomfort containing cresol.*

"Do not use in children under 6 years of age unless recommended by a dentist or physician."

f. *For all drug products for the relief of oral discomfort containing eugenol.*

"Do not use if you are allergic to eugenol."

g. *For all drug products for the relief of oral discomfort containing "caine" derivatives.*

"Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

h. *For OTC drug products containing oral mucosal analgesic active ingredients*—(1) *For oral mucosal analgesics (topical anesthetics) for teething pain.*

"Fever and nasal congestion are not symptoms of teething, and may indicate the presence of infection. If these symptoms persist, consult your physician."

(2) *For oral mucosal analgesics (topical anesthetics) in denture adhesive products.*

"See your dentist as soon as possible."

i. *For OTC drug products containing agents for the relief of toothache*—(1) *For all agents for the relief of toothache.*

(a) "A dentist must be seen as soon as possible whether or not the pain is relieved."

(b) "Toothaches and open cavities indicate serious problems which need prompt attention by a dentist."

(2) *For agents for the relief of toothache intended for use in an open tooth cavity.*

"Use only in teeth with persistent, throbbing pain."

(3) *For agents for the relief of toothache in a dental poultice dosage form.* (a) "Do not instill in tooth cavity."

(b) "Do not apply to irritated oral soft tissue. Use only on healthy tissue."

j. *For OTC drug products containing tooth desensitizer active ingredients.* (1) "Do not continue use beyond 2 weeks except under supervision of a dentist."

(2) "Sensitive teeth may indicate a serious problem which needs prompt care by a dentist."

(3) "See your dentist as soon as possible whether or not relief is obtained."

5. *Packaging.* The Panel recommends packaging restrictions for several OTC drug products for the relief of oral discomfort. Limitation of package size is recommended for the following products in view of safety considerations discussed elsewhere in this document.

a. Products containing benzoin preparations (benzoin tincture and compound benzoin tincture) should be packaged in well-closed containers of 30 mL or less and should have child-resistant caps.

b. Products containing benzyl alcohol should contain no more than 0.6 mL (30 mL of a 2-percent solution or 60 mL of a 1-percent solution) of benzyl alcohol in a container capable of maintaining stability of the product.

c. Products containing butacaine sulfate should be packaged in single-use units to contain no more than 30 mg of butacaine sulfate each with no more than six units per package.

d. Products containing capsicum for use as a counterirritant should be packaged to contain no more than eight applications.

e. Fluoride-containing dentifrices should not contain more than 260 mg total fluorine.

D. *Principles Applicable to Combination Products.*

1. *General combination policy.* The Panel believes that the interests of the consumer are best served by exposing a user of OTC drugs to the fewest ingredients and the lowest dosage that will provide a satisfactory level of effectiveness. Single-component OTC drugs are preferable because they afford a lower risk of undesirable side effects and permit more precise treatment of individual symptoms. The Panel recognizes that there may be a reason for combining active ingredients in certain OTC drugs; however, such combinations must be based on a sound

and logical scientific rationale. The Panel applied the OTC drug review regulation (21 CFR 330.10(a)(4)(iv)) in developing a combination policy for dentifrice and dental care drug products.

The Panel recommends that a product may contain no more than two Category I dentifrice and dental care agent active ingredients that meet the regulatory requirements as well as the criteria adopted by the Panel, together with suitable inactive ingredients, provided that (a) the active ingredients are safe and effective and do not antagonize the therapeutic usefulness of each other, (b) the inactive ingredients are safe and do not interact with or otherwise inhibit the effectiveness of the active ingredients, (c) there is a significant target population that has a single symptom or concurrent symptoms and can thus benefit from use of the combination, (d) use of the combination does not decrease the safety due to adverse effects over use of the single ingredient, and (e) the combination contains adequate directions for use and is labeled with adequate warnings against unsafe use.

The Panel found that some OTC dentifrice and dental care drug products contain combinations of active ingredients both from the same and from different pharmacotherapeutic groups. The Panel is not convinced that combinations containing two or more relief of oral discomfort agents from the same pharmacotherapeutic group with the same mechanism of action would be more effective than the single ingredient alone. Further, combining full therapeutic concentrations of two or more ingredients for the relief of oral discomfort from the same pharmacotherapeutic group with the same mechanism of action may incur unwarranted additional risk.

The alternative to combining two ingredients from the same pharmacotherapeutic class with the same mechinism of action at each ingredient's effective dose is to combine subtherapeutic doses of the ingredients on the theory that such a combination will reduce the risk of side effects or adverse reactions. The Panel prefers full concentrations of single ingredients because it is not aware of any data to support the use of two ingredients with the same mechanism of action in subtherapeutic doses. Combinations containing ingredients of the same pharmacotherapeutic group with the same mechanism of action at less then the minimum effective concentration for any one of the ingredients are, therefore, classified in Category II.

The Panel recognizes that relief of oral discomfort drug products have also been combined with active ingredients from other pharmacotherapeutic groups. The Panel has reviewed and classified combinations of active ingredients for the relief of oral discomfort with active ingredients for the treatment of oral mucosal injury, as discussed below.

The Panel is aware that active ingredients for the relief of oral discomfort have also been combined with oral antiseptic active ingredients, which have been reviewed by the Advisory Review Panel on OTC Oral Cavity Drug Products, and with denture adhesives, which are being reviewed by the Bureau of Medical Devices. These combination products were reviewed and classified by this Panel as to their rationale for concurrent therapy.

The same general principles apply when an active ingredient from a different pharmacotherapeutic group reviewed by another OTC drug advisory panel is combined with an active ingredient of a pharmacotherapeutic group reviewed by this Panel. The rationale for such combinations should be evaluated by FDA according to the combination policy set forth in the reports of both panels.

2. *Limitation of ingredients in combination products.* The Panel recommends that not more than two dentifrice and dental care agent active ingredients be included in any combination product because the addition or more ingredients would increase the risk to the consumer without increasing the benefit.

3. *Labeling of active ingredients.* Labeling for the combination product must conform to the recommended labeling for each active ingredient, and must specify any additional information such as drug interactions or adverse reactions that occur with the combination products, but not with the individual ingredients used alone. The labeling for a Category I combination product should stress that the product should be used only when all symptons are present. The product's labeling should not induce the consumer to take a combination drug when a single entity is appropriate and effective. The consumer should be adequately informed, through the labeling, of the total therapeutic capabilities of the product.

4. *Criteria for Category I combination products.* The Panel recommends the following general criteria for Category I combination drug products for the relief of oral discomfort.

The Panel recommend that each claimed active ingredient in a combination product must make a statistically significant contribution to the claimed effect or effects of the product.

Two Category I active ingredients from different pharmacotherapeutic groups may be combined to treat different symptons concurrently if each Category I active ingredient is present within its established dosage range; the combination is rational; there is a significant target population that suffers from the concurrent symptons; and the combination is as safe and as effective as each individual active ingredient used alone.

5. *Category I combination drug products for the relief of oral discomfort.* The Panel recommends that the following combinations be classified as Category I for the relief of oral discomfort.

a. *Combination of two agents for the relief of oral discomfort (an oral mucosal protectant and an oral mucosal analgesic).* One Category I oral mucosal protectant may be combined with one Cagetory I oral mucosal analgesic. An oral mucosal protectant protects the affected area from a pain stimulus, and an oral mucosal analgesic provides relief in pain. These two agents complement each other when used in the same dosage form, and both are intended to remain on the wound.

b. *Combinations of an agent for the relief of oral discomfort with an oral antiseptic.* (Reviewed by the Advisory Review Panel on OTC Oral Cavity Drug Products.)

(1) *Oral mucosal protectant and an oral antiseptic.* The Panel finds that this combination is rational and will provide the patient with additional protection against further irritation and infection. The oral mucosal protectant will provide a coating over the wound and hold the antiseptic agent in place where it can act most effectively.

(2) *Oral mucosal analgesic and an oral antiseptic.* The Panel finds that this combination is rational. Pain may frequently accompany minor oral wounds, and treating the discomfort and preventing possible infection concurrently is a convenient and reasonable approach to therapy.

(3) *Oral mucosal protectant, oral mucosal analgesic, and an oral antiseptic.* The Panel finds that this combination is rational. An oral mucosal analgesic provides relief of pain, the oral mucosal protectant provides a coating over the wound, and the antiseptic agent is held in place where it can act most effectively.

c. *Combination of an agent for the relief of oral discomfort and a denture adhesive.* (Under review by the Bureau of Medical Devices.)

Oral mucosal analgesic and a denture adhesive. The Panel finds that this combination is rational. Immediate dentures, particularly, may be uncomfortable or painful in some instances. Combining an oral mucosal analgesic with a denture adhesive may enable the denture wearer to benefit from the analgesic action, while the adhesive helps to secure the dentures, and both actions increase the comfort of the user.

6. *Criteria for Category II combination products.*

The Panel recommends the following criteria for Category II combination drug products for the relief of oral discomfort.

a. A combination is Category II if a Category II active ingredient or Category II labeling is present in the combination product.

b. A combination product containing Category I or Category III active ingredients from the same pharmacotherapeutic group with the same mechanism of action is classified as Category II.

c. A combination product containing active ingredients from different pharmacotherapeutic groups is classified as Category II if it includes any ingredient in less than the minimum effective concentration established by the Panel.

d. If a combination contains an active ingredient or other condition that has not been reviewed by this or any other OTC drug advisory review panel, such ingredient or condition is Category II and the resulting combination then becomes Category II.

e. A combination product is classified as Category II if it includes more than two dentifrice and dental care agent active ingredients.

f. A combination product is classified as Category II if it contains active ingredients from more than one pharmacotherapeutic group and there is not a significant target population that has a concurrent need for a drug from each of these groups.

g. A combination of two Category I active ingredients from different pharmacotherapeutic groups is Category II if the ingredients cannot be combined because of chemical or physical formulation problems that would result in decreasing the safety or effectiveness of the individual ingredients.

7. *Category II combination drug products for the relief of oral discomfort.* The Panel recommends that the following combinations be classified as Category II for the relief of oral discomfort.

a. *Combinations of two agents for the relief of oral discomfort*—(1) *Oral mucosal protectant and an agent for the relief of toothache.* The Panel finds no rationale for such a combination. These two agents are intended to be applied at different sites in the oral cavity and to treat symptoms resulting from different etiologies. Further, if administered in a combination product, the oral wound protectant might obstruct the tooth cavity and prevent the escape of gases and fluids. The Panel considers such an obstruction to be detrimental and dangerous to the health of the consumer.

(2) *Oral mucosal protectant and a counterirritant.* The Panel finds no rationale for such a combination; such ingredients are, in fact, therapeutically antagonistic. By definition, a counterirritant is irritating, and such an agent should not be applied to injured tissue either alone or in combination with a wound protectant.

(3) *Oral mucosal protectant and a tooth desensitizer.* The Panel finds no rationale for such a combination. These pharmacotherapeutic agents are intended to be applied at different sites and to treat symptoms resulting from different etiologies.

(4) *An agent for the relief of toothache intended to be used in an open tooth cavity and a counterirritant.* The Panel finds no rationale for such a combination. By definition, a counterirritant is irritating, and should never be placed in the tooth cavity. Such irritating agents therefore should not be used in combination with an agent intended to be used in an open tooth cavity to provide toothache relief.

(5) *An agent for the relief of toothache and a tooth desensitizer.* The Panel finds no rationale for such a combination. These pharmacotherapeutic agents are intended for application to different sites and to treat symptoms resulting from different etiologies.

(6) *Oral mucosal analgesic and an oral mucosal analgesic, both from the same group with the same mechanism of action.* The Panel concludes that any combination of two oral mucosal analgesics from the same group with the same mechanism of action, at full or less than full therapeutic concentrations, is Category II. This includes the combination of two "caine" or the combination of two aromatic analgesics. The weight of scientific evidence is against such combinations (Ref. 1).

(7) *Oral mucosal analgesic and a tooth desensitizer.* The Panel finds no rationale for such a combination. These pharmacotherapeutic agents are intended to be applied at different sites, and are for the relief of different types of painful symptoms with different etiologies.

(8) *A counterirritant and a counterirritant.* The Panel finds no rationale for such a combination and prefers a single-ingredient product.

(9) *A counterirritant and a tooth desensitizer.* The Panel finds no rationale for such a combination. These pharmacotherapeutic agents are intended to be applied at different sites. Irritating chemicals should not be applied to exposed dentin.

b. *Combinations of an agent for the relief of oral discomfort with an oral mucosal injury agent*—(1) *Oral mucosal protectant and an oral wound cleanser.* The Panel finds no rationale for such a combination. An oral mucosal protectant forms a protective film over the area to which it is applied. The use of an oral wound cleanser in the same dosage form with an oral mucosal protectant would result in the cleanser removing the protectant from the affected area, thus making the protectant ineffective.

(2) *An agent for the relief of toothache and an oral wound cleanser.* The Panel finds no rationale for such a combination. If an agent for the relief of toothache is administered in the same dosage form with an oral wound cleanser, the agent for the relief of toothache will be removed from its site of action when the oral wound cleanser is expectorated and, thus, before it has had an opportunity to exert its intended pharmacotherapeutic effect. These two pharmacotherapeutic agents are intended to be used at different sites in the oral cavity.

(3) *Oral mucosal analgesic and an oral wound cleanser.* The Panel finds no rationale for such a combination. If an oral mucosal analgesic is administered in the same dosage form with an oral wound cleanser, the oral mucosal analgesic will be removed from its site of action when the oral wound cleanser is expectorated. These two pharmacotherapeutic agents are intended to be used sequentially and not at the same time.

(4) *Counterirritant and an oral wound cleanser.* The Panel finds no rationale for such a combination. By definition, a counterirritant is irritating, and such an agent should not be used when cleansing a wound.

(5) Tooth desensitizer and an oral wound cleanser. The Panel finds no rationale for such a combination.

(6) *An agent for the relief of toothache and an oral wound-healing agent.* An oral wound-healing agent is intended for use on mucosal tissue, not on tooth pulp. An agent for the relief of toothache is intended for use on irreversibly damaged pulp and should only be used when there is no possibility that the pulp injury is reversible. Hence, an oral

wound-healing agent would confer no benefit when applied to tissue that has no potential for healing.

(7) *Counterirritant and an oral wound-healing agent.* The Panel finds no rationale for such a combination. By definition, a counterirritant is irritating, and such an agent should not be used on a healing wound.

(8) *Tooth desensitizer and an oral wound-healing agent.* The Panel finds no rationale for such a combination. These two pharmacotherapeutic agents are intended to be used at different sites in the oral cavity.

(9) *Oral mucosal protectant and a peroxide-containing oral wound-healing agent.* The Panel finds no rationale for such a combination. If an oral mucosal protectant is administered in the same dosage form with a peroxide-containing oral wound-healing agent, the bubbling action of the peroxide would remove the protectant from the site of action before it has had an opportunity to exert the intended pharmacotherapeutic effect.

(10) *Oral mucosal analgesic and a peroxide-containing oral wound-healing agent.* The Panel finds no rationale for such a combination. If an oral mucosal analgesic is administered in the same dosage form with a peroxide-containing oral mucosal analgesic, the bubbling action of the peroxide would remove the analgesic from the site of action before it has had an opportunity to exert the intended pharmacotherapeutic effect.

c. *Combinations of an agent for the relief of oral discomfort with an oral antiseptic.* (Reviewed by the Advisory Review Panel on OTC Oral Cavity Drug Products.)

(1) *An agent for the relief of toothache and an oral antiseptic.* The Panel finds no rationale for such a combination. The oral antiseptic will not contribute to the relief of toothache, nor is any infection within the tooth controllable by applying an antiseptic.

(2) *A counterirritant and an oral antiseptic.* The Panel finds no rationale for such a combination. A counterirritant must only be applied to normal oral mucosa. Since no infection is present at the site of use, no antiseptic is needed.

(3) *A tooth desensitizer and an oral antiseptic.* The Panel finds no rationale for such a combination. A tooth desensitizer is applied by brushing and is not applied at the site of an infection. It would be irrational either to use an antiseptic in the absence of any infection or to apply an antiseptic in a dosage form that must be brushed onto the site of application.

d. *Combinations of an agent for the relief or oral discomfort with a denture adhesive.* (Under review by the Bureau of Medical Devices.)

(1) *An oral mucosal protectant and a denture adhesive.* The Panel finds no rationale for such a combination. An oral mucosal protectant forms a film over the area to which it is applied. Such a film would interfere with the action of the adhesive. The added thickness of the oral wound protectant would also interfere with the fit of the dentures and could be expected to cause further injury or irritation as a result.

(2) *An agent for the relief of toothache and a denture adhesive.* The Panel finds no rationale for such a combination. These two agents are intended to be applied at different sites in the oral cavity.

(3) *A counterirritant and a denture adhesive.* The Panel finds no rationale for such a combination. By definition, a counterirritant is irritating, and such an agent should not be used under dentures.

(4) *A tooth desensitizer and a denture adhesive.* The Panel finds no rationale for such a combination. These two agents are intended to be applied at different sites in the oral cavity.

8. *Criteria for Category III combination products.* The Panel recommends the following criteria for Category III combination drug products for the relief of oral discomfort.

a. If a Category III active ingredient or other condition is present in a combination product containing no Category II ingredient or labeling the combination is classified as Category III.

b. If two agents for the relief of oral discomfort from the same pharmacotherapeutic group, but with different mechanisms of action, are present in a combination drug product, that combination is classified as Category III.

9. *Category III combination drug products for the relief of oral discomfort.* The Panel recommends the following combinations be classified as Category III for the relief of oral discomfort.

a. *Combination of two agents for the relief of oral discomfort*—(1) *Oral mucosal protectant and an oral mucosal protectant.* The Panel did not review any data relating to such combinations. However, the Panel believes that there may be a rationale for combining two such agents. Data must be generated to establish that each ingredient makes a contribution to the claimed effect without decreased effectiveness or safety.

(2) *A tooth desensitizer and a tooth desensitizer.* There may be a rationale for combining two such agents. However, the data reviewed by the Panel relating to such combinations did not establish that each ingredient makes a contribution to the claimed effect.

b. *Combinations of an agent for the relief of oral discomfort with certain oral mucosal injury agents*—(1) *Oral mucosal protectant and an oral wound healing agent.* These two types of agents may be combined provided testing is performed to establish that the oral mucosal protectant does not interfere with the action of the oral wound healing agent. The protectant will hold the oral wound healing agent in place at the site of the wound, and will also protect the wound from further injury and irritation.

(2) *Oral mucosal analgesic and an oral wound healing agent.* The oral mucosal analgesic will provide relief of the symptoms of pain or discomfort while the oral wound healing agent promotes healing.

(3) *Two agents for the relief of toothache acting by different mechanisms.* Agents for the relief of toothache may act by different mechanisms. For example, benzocaine and butacaine are Category III agents for the relief of toothache and would act by producing surface anesthesia, while eugenol is a Category I agent for the relief of toothache and probably obtunds toothache by a different mechanism (Ref. 2).

(4) *An agent for the relief of toothache and an oral mucosal analgesic.* Since some oral mucosal analgesics are also agents for the relief of toothache, they may be combined under the conditions described under (3) above for the relief of toothache but not for use as oral mucosal analgesics.

(5) *An oral mucosal analgesic and a counterirritant.* The only counterirritant acceptable to the Panel in Category III is capsicum. Capsicum is used to provide relief of toothache pain in a poultice dosage form applied between the cheek and the gum, and should only be applied to intact, nonirritated mucous membrane. Capsicum has been combined in poultices with the oral mucosal analgesic benzocaine.

(6) *Two oral mucosal analgesics acting by different mechanisms.* Oral mucosal analgesics may act by different mechanisms, e.g., benzocaine (a "caine") and phenol (an aromatic). Therefore, it may be rational to combine them at full or less-than full dosage.

c. *Combinations of an oral mucosal protectant with an oral mucosal analgesic claiming a prolonged duration of action.*

Oral mucosal protectants may hold an oral mucosal analgesic in contact with the affected area for a longer period of

time than if the oral mucosal analgesic were applied as a single active ingredient. This effect, however, has not been proven for any combination.

Data must be generated to establish that such a combination significantly prolongs the duration of action of the oral mucosal analgesic without decreasing the safety or effectiveness of either ingredient. Any claim of this longer duration of action due to the combination must be proven, and the Panel recommends that such a claim be classified as Category III.

References

(1) Adriani, J., and R. Zepernick, "Clinical Effectiveness of Drugs Used for Topical Anesthesia," *Journal of the American Medical Association*, 188:711–716, 1964.

(2) Bender, I. B., presentation to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 14th meeting, October 16–17, 1974.

E. Statement on Category III Testing Procedures

1. *Comments on study design.* The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III active ingredient into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved technology in the future.

Experimental design should take into account the need to include a sufficient number of subjects or trials so as to provide meaningful conclusions which can be supported by appropriate statistical analysis. The selection of appropriate subjects or patients can be a major importance when the effect of a drug in a specific illness or symptom is under study.

Some bias may exist in all situations wherein the subject, the observer, or both make a judgment as to the nature or magnitude of a response. Biological factors also contribute to variation in response between individuals in a given study sample. Although bias and biological variation cannot be eliminated, their effect on the outcome of an experiment can be minimized by adopting a "double-blind, placebo-controlled" or other suitably blinded design. In such a design, one group of subjects receives a placebo so that the placebo response, unmodified by the conditioning of the test, can be established. Whenever possible, neither the subjects nor the observer should be able to distinguish the identity of the preparations under test. This requires that the test preparations and placebos be indistinguishable in regard to shape, color, odor, and taste. However, in the case of preparations containing active volatile agents or substances which affect sensory perception, it is impossible to make the placebo indistinguishable from active ingredients. When a placebo is used for comparison, the medication should exert a quantitatively positive effect which is statistically significant when compared to the placebo. The level of statistical significance which is acceptable is described under each Category III protocol. (See paragraph C. of parts III., IV., V., and VI. below—Data Required for Evaluation.)

It is often desirable to include, as a positive control, a standard drug which is known to exert a significant effect against the relevant symptoms being tested. When a standard drug is used for comparison, the test medication should be at least equivalent to the standard.

Finally, the inclusion of two or more dose levels (or concentrations) of the drug under test may be desirable in order to provide an estimate of an effective therapeutic dose range which is free from undesirable side effects. If a crossover design is utilized, i.e., each subject serves as his or her own control, the sequence in which the placebo, standard, and test drugs are administered should be randomized and a sufficient "wash-out period" between tests should be permitted.

Wherever possible, objective measurements should be made in preference to subjective judgments. However, subjective measurements may be required if relevant to the symptom or symptom complex for which the drug under test is to be used.

2. *Testing period provided for Category III conditions.* The Panel has determined that the available data are insufficient (Category III) to classify some conditions either as Category I or Category II. Such conditions are permitted to remain on the market, or to be introduced into the market, after the date of publication of the final monograph in the **Federal Register**, provided that FDA receives notification of testing in accordance with § 330.10(a)(13) (21 CFR 330.10(a)(13)). The Panel recommends that Category III conditions should be tested within 2 years except as noted for specific pharmacotherapeutic groups.

3. *Testing guidelines for Category III combination products.* The Category III active ingredients for the labeling indication claims must be tested in accordance with the evaluation protocol specified for that particular pharmacotherapeutic classification. If, when tested alone, the Category III ingredient or ingredients can be shown to be safe and effective in accordance with the standards for evaluation established in the protocols, it will then qualify for Category I status. The combination will then contain only Category I active ingredients, but still must be tested to prove that each ingredient makes a contribution to the product's claimed effect(s).

An acceptable test procedure will be one in which the proposed combination and each of the individual active ingredients at the proposed dosage level in the combination are evaluated, all in the same study, and compared to a placebo for effectiveness against the relevant labeling claim. In this way it can be shown whether or not each active ingredient in the combination makes a contribution toward effectiveness without incurring an unnecessary decrease in safety.

F. Drug Misuse and Abuse

The potential for development of drug tolerance and addiction due to the use of dentifrices and dental care agents, even when the patient is on an unsupervised regimen, does not seem to exist. However, the Panel believes that misuse of dental care agents occurs when an agent tends to give the subject a false sense of security, thereby diminishing his desire to seek professional advice. When this possibility exists, the label warnings should alert the patient to this danger.

Several products, such as denture adhesives combined with oral mucosal analgesics and agents for the relief of toothache, discussed elsewhere in this document, are excellent examples of drug products which might be subject to misuse. The problem becomes especially acute when signs of an infection or other symptoms are subdued but the underlying cause is not corrected or if a subject, needing professional dental care, uses an OTC dental care drug product to enable him or her to postpone the needed care. Labeling of OTC dentifrice and dental care drug products should include warnings against possible misuse of the specific ingredients.

G. Pediatric Considerations

The Panel reviewed the conditions under which dental care products can be safely used by children. Children are defined by the Panel as persons under 12 years of age. Many of the active ingredients reviewed by the Panel as drug products for the relief of oral discomfort have different indications, dosages, and directions for different age groups. For specific information on the labeling of individual active ingredients, see the labeling discussions elsewhere in this document. (See paragraph B.1. of

parts III., IV., V., and VI. below—Category I Labeling.)

The Panel considered the acute and chronic toxic effects of fluoride ingestion in determining whether drug products containing fluoride can be safely used by children. The Panel's recommendations for the use of these products by children are included in the preamble to the proposed monograph on anticaries drug products in the section entitled "Pediatric Considerations" (45 FR 20673; March 28, 1980). The proposed monograph on anticaries drug products (hereinafter referred to as the anticaries report) was published in the **Federal Register** of March 28, 1980 (45 FR 20666). The panel's recommendation concerning package size limitations and child-resistant closures for anticaries drug products are equally applicable to fluoride drug products used as tooth desensitizers.

Package size limitations have also been recommended for benzoin preparations and benzyl alcohol. The Panel recommends that benzoin preparations, which are Category I oral mucosal protectants, be packaged in containers of not more than 30mL compound benzoin tincture or 30 mL benzoin tincture and that the packages have child-resistant closures.

The Panel recommends that benzyl alcohol, which is a Category III oral mucosal analgesic and an agent for the relief of toothache, be packaged in containers which contain no more than 0.6 mL of benzyl alcohol. Animal studies suggest that ingestion of benzyl alcohol (1 mL/kg) may be fatal (Ref. 1). Package sizes that will provide more than 30 mL of a 2-percent solution of 60 mL of a 1-percent solution are unnecessary and may be a potential risk for accidental ingestion by young children.

Benzocain was reviewed by the Panel and is recommended for classification as a Category I oral mucosal analgesic and a Category III agent for the relief of toothache. The Panel is aware that benzocaine in high doses may cause methemoglobinemia, because it can interfere with the reconversion of methemoglobin to hemoglobin (Refs. 2 and 3.) Most reported systemic reactions reviewed by the Panel were in infants under 6 months of age (Refs. 4 throught 7). Infants may be more susceptible due to a deficiency of DPNH (diphosphopyridine nucleotide)-dependent methemoglobin reductase which protects against methemoglobin-inducing foreign compounds (Ref. 7). Infants under 4 months of age, who may have not as yet developed sufficient quantities of the reductase, develop methemoglobinemia more easily than older children and adults. The Panel has, therefore, recommended that infants under 4 months of age should not be treated with benzocaine except under the advice and supervision of a dentist or physician. No specific warning concerning methemoglobinemia is considered necessary.

The Panel has also recommended that children under 12 years of age should be supervised in the use of benzocaine-containing dental products.

References

(1) Macht, D. I., "A Pharmacological and Therapeutic Study of Benzyl Alcohol as a Local Anesthetic," *Journal of Pharmacology and Experimental Therapeutics*, 11:263–279, 1918.

(2) Adriani, J., and R. Zepernick, "Clinical Effectiveness of Drugs Used for Topical Anesthesia," *Journal of the American Medical Association*, 188:711–716, 1964.

(3) Swinyard, E. A., "Local Anesthetics," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by A. Osol et al., Mack Publishing Co., Easton, PA, p. 987, 1975.

(4) Hughes, J. R., "Infantile Methemoglobinemia Due to Benzocaine Suppository," *Journal of Pediatrics*, 66:797–799, 1965.

(5) Peterson, H. C., "Acquired Methemoglobinemia in an Infant due to Benzocaine Suppository," *New England Journal of Medicine*, 263:454, 1960.

(6) Bloch, A., "More on Infantile Methemoglobinemia Due to Benzocaine Suppository," *Journal of Pediatrics*, 67:509–510, 1965.

(7) Wolff, J. A., "Methemoglobinemia Due to Benzocaine," *Pediatrics*, 20:915–916, 1957.

H. Inactive Ingredients

The Panel is aware of the need for the inclusion of inactive ingredients in OTC drug products for the relief of oral discomfort. Preferably, these should be limited to agents that are considered necessary such as abrasives, preservatives, aromatics, vehicles, colorants, sweeteners, antioxidants, buffers, and agents required for particular dosage forms.

The Panel did not undertake an extensive review of inactive ingredients, because it is the view of this Panel that the safety and the advisability of including specific inactive ingredients in drug products should be reviewed by an appropriate Panel. Since many of these ingredients are used in the formulation of many drug products other than those reviewed by this Panel, it is not appropriate that they be dealt with specifically and solely in relation to dentifrices and dental care agents for the relief of oral discomfort.

The Panel recommends that in view of the inactive ingredients, such as sodium lauryl sarcosinate, which have caused oral mucosal irritation, the final formulation of OTC drug products for the relief of oral discomfort should be shown to be safe and nonirritating. Monitoring of consumer complaints should detect, at an early stage, irritation or allergic manifestations not detectable in animal studies.

I. Single Active Ingredient Products

The Panel has discussed dental combination products earlier in this document. (See part II. paragraph D. above—Principles Applicable to Combination Products.) The Panel believes there are some combinations which may be rational for concurrent therapy of multiple symptoms for a significant portion of the target population. However, for the individual who has only one symptom and who may need only one ingredient, single active ingredients afford the opportunity to selectively treat such a condition.

Great variability with regard to side effects induced by drugs is seen among patients. Although these effects and the drugs producing them are sometimes familiar to dentists, physicians, and pharmacists, when the ingredient is present in a combination, it may be difficult to identify the ingredient causing the side effect. Furthermore, use of fixed combinations for the treatment of a particular symptom, where a single ingredient product would be safe and effective, exposes the consumer to additional risk of side effects, idiosyncratic reactions, and allergenicity without added benefit. These difficulties are largely avoided with single active ingredients, which many dentists and pharmacists prefer to recommend. There was agreement among Panel members that the availability of products containing single active ingredients would provide increased opportunity for the public and health professionals to select products appropriate to treat the symptoms.

J. General Statements on the Determination of Safety and Effectiveness for OTC Dental Products

The Panel evaluated the safety and effectiveness of OTC dental active ingredients as well as proper dosage ranges for OTC drug use. In reviewing the scientific literature for these ingredients, the Panel evaluated the available data as to whether or not the ingredient was safe and effective. Among those agents determined to be safe and effective, the Panel did not attempt to determine the drugs of choice for any particular indication.

1. *Determination of safety.* In deciding on the safety of a drug or combination of drugs for the intended use, both animal and human studies were considered. The animal data were usually related to

levels of the drug that might cause death or serious adverse effects on vital tissues such as the bone marrow, liver, and kidneys. Also, the possibility that the drug might cause adverse effects on teeth or irritation of the oral mucosa was evaluated. Animal studies were helpful in establishing benefit-to-risk ratios for ingredients which are commonly used.

Major attention was paid to information related to adverse drug effects in humans, both adults and children. A knowledge of the toxicology of the drug or drugs under consideration both in animal studies and from human experience makes it possible to look specifically for adverse effects in one or more organs or systems. For example, manufacturers of topical anesthetics were required to show that the ingredients used in their products were safe when such ingredients were used in effective concentrations.

It was desirable that there be studies in which the drug was evaluated in its final composition and compared to its vehicle control. However, there were times when the Panel was called upon to make judgments without benefit of controlled pharmacological studies, since they were not available for some ingredients.

2. *Determination of effectiveness.* In determining effectiveness for the intended use. the Panel considered separately each pharmacotherapeutic group under review although certain general principles apply to all groups.

In terms of effectiveness, animal studies were seldom very helpful since it is difficult to find animal models which closely mimic the course of oral diseases and conditions in humans.

Major attention was paid to clinical studies, especially where the double-blind technique could be employed. The inclusion of a placebo as a comparison was considered desirable and comparison of the agent with a known standard was also considered useful.

Studies utilizing objective measurements, proper controls, and statistical analysis carried considerable weight in the Panel's decision to place an ingredient in Category I. Clinical experience of a general nature, if documented by qualified experts, added somewhat to the final decisions.

The Panel recognizes the extensive marketing history of many dental preparations. Members of the drug industry presented data to the Panel summarizing their marketing history and consumer complaint information. The effectiveness of such products may never have been subjected to scientific investigation even though the products have been marketed for many years. Apparent consumer acceptance and testimonial data used by many manufacturers as the sole evidence of effectiveness and safety were not acceptable to the Panel. When claims of effectiveness were supported solely by outdated experimental methodology, this evidence for effectiveness was also considered unacceptable.

The Panel took into account the marketing experience of manufacturers as stated in their submissions. Although the Panel found these data helpful, marketing experience neither overruled nor substituted for the Panel's other sources of knowledge of safety, effectiveness, and rationale for such products.

SUMMARY OF THE PANEL'S CATEGORIZATION OF ACTIVE INGREDIENTS

Active ingredients	Oral mucosal protectant	Agent for the relief of toothache	Tooth desensitizer	Oral mucosal analgesic	Counter-irritant
Benzocaine		III(E)		I	
Benzoin preparations (benzoin tincture and compound benzoin tincture)	I				
Benzyl alcohol		III(SE)		III(SE)	
Butacaine sulfate		III(SE)		I	
Camphor				II(SE)	
Capsicum		II(SE)			III(E).
Citric acid and sodium citrate in poloxamer 407			III(E)		
Creosote		III(SE)			
Cresol		III(SE)		III(SE)	
Eugenol preparations (85 to 87 percent eugenol in clove oil or a bland, fixed oil)		I			
Eugenol (1 to 84 percent)		III(E)			
Fluoride preparations (sodium fluoride, sodium monofluorophosphate, and stannous fluoride)			III(E)		
Formaldehyde solution			III(E)		
Menthol		II(S)			
Methyl salicylate		II(SE)		II(SE)	
Myrrh, fluidextract	III(SE)				
Phenol preparations (phenol and phenolate sodium)		III(SE)		I	
Potassium nitrate			III(E)		
Sodium fluoride, strontium chloride, and edetate disodium			II(SE)		
Strontium chloride			III(E)		
Thymol preparations (thymol and thymol iodide)		III(E)		III(E)	

(S) = placed in indicated category for safety considerations.
(E) = placed in indicated category for effectiveness considerations.
(SE) = placed in indicated category for both safety and effectiveness considerations.

III. Agents for the Relief of Toothache

A. General Discussion

Agents for the relief of toothache provide temporary relief of pain arising as a result of an open tooth cavity. All agents for the relief ot toothache, except counterirritants, are applied into an open tooth cavity. Counterirritants are applied in a dental poultice to the gingiva surrounding a tooth with a painful pulpitis. Agents for the relief of toothache have been on the market for a long period of time; they probably had their origin in empiric medicine.

1. *Agents for the relief of toothache applied into an open tooth cavity.* It is now known that the dental pulp is very susceptible to irritation. Some causes of irritation are dental caries, excessive heat, and placement of irritating chemicals or filling materials in a deep cavity. Irritation causes inflammation in the pulp which can be divided into reversible and irreversible stages. During the reversible stage, the application of medication resulting in added irritation or dehydration of dentin may cause the damage of the pulp to reach the irreversible stage, rendering the tooth nonviable. Dehydration is damaging because it increases the permeability of the dentinal tubular contents. Thus, in general, any agent which irritates or dehydrates dentin is considered unsafe if applied during the reversible stage of pulp disease.

The dental profession has voiced considerable concern about the safety and effectiveness of agents for the relief of toothache (Ref. 1). The Panel

reviewed complaints about various dental products from a variety of sources. In brief, many dentists and dental organizations expressed concern that agents for the relief of toothache can have harmful effects and that their effectiveness is doubtful (Refs. 1 and 2).

The Panel called upon two expert consultants to provide their opinions on agents for the relief of toothache. These consultants were not in complete agreement; however, their opinions, based on their own and others' research and practice, were very helpful to the Panel (Refs. 3 and 4).

After studying the consultants' reviews and comments, and after reviewing the submissions and other pertinent literature, the Panel came to the following conclusions:

a. Most toothache remedies are very caustic preparations which will burn the oral mucosa. These burns heal rapidly so the consequences of this adverse effect are not severe. Of greater concern is the effect of these irritant chemicals on dentin and viable dental pulp.

b. The systemic effect of toothache remedies is generally not considered to be of consequence since only minute amounts of the drugs are used. Corticosteroids, which do have systemic effects, are limited to use by the dentist or physician. The Panel recognizes that any drug to which the subject is intolerant or allergic may be harmful even when applied in small quantities.

c. The main effect of OTC agents for the relief of toothache is probably as a placebo. Most of these preparations have a "medicinal" taste and smell and are irritants. These properties distract the patient and may provide some psychological feeling of benefit, but the major problems of deep caries, pulpitis, and infection remain untreated.

c. Irritants or agents instilled in the tooth cavity which excessively dehydrate the tooth structure (such as high concentrations of alcohols) can do harm to any pulp which as reversible damage, but cannot do further injury to the irreversibly damaged pulp. Ethyl alcohol above 20 percent is considered to be an irritant to the dental pulp and, therefore, should not be used above 20 percent in agents for the relief of toothache which are to be used in an open tooth cavity.

It is irrational to place a substance into a tooth cavity which may occlude the opening through which an abscess may drain allowing fluid and gas to escape. Cotton soaked with medication, waxes, or gums are occulsive agents. Agents which harden and form a filling, such as sandarac, may be especially detrimental. Occulsion of the cavity may intensify pain and promote the spread of infection to deeper tissues. Agents which occlude the cavity are, therefore, unacceptable.

The Panel recognizes that the ingredients beeswax and sandarac are inactive. However, the Panel feels that the use of occlusive agents such as these in a tooth cavity for the relief of toothache pain exposes the consumer to unnecessary safety risks. The Panel recommends that agents for the relief of toothache shall not contain any agent which acts as a physical barrier and does not permit the escape of fluids and gases from a degenerating pulp (Refs. 5 and 6). Blockage of the drainage from a cavity by ingredients such as beeswax and sandarac may result in increased pain and possible spread of infection.

Beeswax can act as a physical barrier in the tooth cavity. Sandarac is a resin which is soluble in alcohol, but insoluble in water. It is utilized as a component of certain cavity varnishes for professional application in dentistry. In OTC products for the relief of toothache, sandarac in alcoholic solution is used to saturate a cotton pellet which is then placed in the open cavity of a carious tooth or a tooth with a lost restoration. In contact with water or oral fluids, the sandarac precipitates, forming with the cotton a temporary filling. Such a temporary filling would, theoretically, protect exposed dental structures from air, food, or thermal changes, thereby decreasing pain originating from these stimuli. However, alcohol used as a solvent for sandarac will denature dentinal tubules and dehydrate dentin (Ref. 5). In addition, a temporary filling applied in a tooth with acute suppurative pulpitis may increase pain by blocking escape of an inflammatory exudate and gases (Refs. 5 and 6). Since the patient cannot reliably determine whether or not there is drainage from the cavity, use a self-applied temporary dental filling is not advisable. The Panel is award that beeswax, sandarac, or other ingredients which may form physical barriers in a tooth cavity may be added as inactive ingredients; however, it is considered unsafe to use these ingredients in such a manner that they do form physical barriers in a tooth cavity for reasons stated above.

The Panel is concerned that other occlusive agents which were not submitted to the Panel for review may be on the market. In this document only beeswax and sandarac are discussed as occlusive agents, but it is the intention of the Panel to recomment that all inactive ingredients which form an occlusive filling in a tooth cavity may not be included in agents for the relief of toothache intended for use in an open tooth cavity.

Because there may be a sufficient target population who could obtain temporary relief from some toothache medication, it would be helpful to have such medications remain on the market with appropriate warnings on the label.

The requirements for safety and effectiveness of agents for the relief of toothache agreed upon by the Panel are as follows:

(a) *Safety requirements for agents for the relief of toothache.* Agents for the relief of toothache should not cause sloughing or necrosis of soft tissue, should have low potential for allergenicity, should not cause a systemic effect, and should not cause irreversible damage to tissues surrounding the end of the root (periapical). In addition, combinations of ingredients including agents for the relief of toothache may be rational if it can be shown that the criteria for combination products can be met. (See part II. paragraph D. above—Principles Applicable to Combination Products.)

(b) *Effectiveness requirements for agents for the relief of toothache.* Agents for the relief of toothache must temporarily relieve the discomfort of a toothache. Although some agents for the relief of toothache may have antiseptic activity, no claims should be made for antiseptic activity because it has not been demonstrated to contribute to the effectiveness of relieving the pain of toothache. In addition, a combination of ingredients may be rational if it can be shown that each ingredient contributes to the temporary relief of discomfort as required in the Panel's combination policy. (See part II. paragraph E. above—Statements on Category III Testing Procedures.)

The Panel concludes that agents which may provide some relief of toothache are clove oil and eugenol at an equivalent concentration (85 to 87 percent) which have an anodyne effect when applied to dentin. These appear to be the best agents for the relief of toothache available and are recommended for Category I status. The Panel felt that oral mucosal analgesics are also possible agents for the relief of toothache discomfort but more data are required. Also, more data are required to test effectiveness of eugenol at lower concentrations than found in clove oil in suitable bland vehicles.

2. *Agents used for the relief of toothache applied in a poultice dosage form.* Counterirritants are irritating drugs that are applied locally to the skin or oral mucosa for the relief of pain originating from a structure other than the cite of application. Usually the counterirritant drug is applied to an area

overlying or adjacent to the deeper site which is perceived to be the origin of the painful stimulus (Ref. 7).

The Panel believes that because of their irritant nature, counterirritants for the relief of toothache should not be utilized in dosage forms intended for instillation into a tooth. Drugs classified as counterirritants, and, in general, other agents with irritant action, if instilled into a tooth cavity will injure a viable pulp. The Panel also concludes that it is irrational to apply a counterirritant to oral soft tissues which are already irritated. However, in order to relieve toothache, an irritant drug might be applied in a dental poultice to the gingiva surrounding a tooth with a painful pulpitis. Dental poultices are topical dosage forms containing medication enclosed within a porous sack. When applied to the oral mucous membrane in the presence of moisture, the dental poultice releases the medication.

The concept of usefulness of counterirritation in relief of pain of muscles, joints, and viscera from local application is widely accepted, even though such acceptance is presently based on empirical observation rather than on rigorous scientific evaluation (Refs. 3 and 7, 8, and 9). At least one counterirritant, capsicum, has had a long history of use in dental products for the relief of toothache and of pain from irritations of the gingiva. No adequate studies are avilable to prove or disprove that a counterirritant is effective in relieving oral hard or soft tissue pain.

The first response to local irritation is an increase in circulation to the site, the vasodilation being accompanied by a feeling of warmth, comfort, and sometimes pruritis (Ref. 8). The following mechanisms of pain relief by counterirritation have been postulated, and one or more of these proposed mechanisms may apply:

Sensory nerve impulses originating from irritation of the skin or mucosa are relayed in the central nervous system (CNS) to the motor nerves of blood vessels, so that increased circulation at the site of action has its counterpart in increased circulation to deeper structures innervated from the same level of the CNS (Refs. 2 and 10).

Sensory impulses arising from irritation of the skin or mucosa produce dilation of blood vessels, such as deeper arterioles, as a result of nerve reflexes (Refs. 10 and 11).

Sensory impulses arising from irritation of the skin or mucosa by the topical application of the counterirritant may alter the characteristics of the deeper sansations perceived as pain (Ref. 2).

The peripheral impulses may occupy a pathway common to both peripheral and deep impulses, resulting in a complete or partial block of those impulses arising from the deeper structures (Refs. 2 and 11).

Pain is a subjective sensation, and if a counterirritant can provide pain relief by any of the postulated mechanisms (except placebo) such pain relief should be measurable. Pain relief would probably be more easily documented if the drug were incorporated into a dosage form such as a dental ointment than if tested in a dental poultice, a dosage form which might contribute a particularly high placebo effect.

The Panel believes that there is a possibility of a dental poultice becoming accidentally lodged in the throat or in the respiratory tract if the user falls asleep with the poultice in place. The Panel, therefore, recommends that the label of products in a dental poultice dosage form carry the warning, "To avoid danger of choking do not leave a poultice in the mouth during periods of sleep." In addition, the Panel recommends the following warnings for counterirritants in a dental poultice dosage form:

"Do not instill in tooth cavity."

"Use only on healthy tissue. Do not apply to irritated oral soft tissue."

References

(1) Skierkowski, P., and N. Burdock, "External Analgesic Products," *in* "Handbook of Nonprescription Drugs," 5th Ed., American Pharmaceutical Association, Washington, p. 289, 1977.

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(3) Bender, I. B., presentation to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 14th Meeting, October 16–17, 1974.

(4) Ellison, R., presentation to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 5th Meeting, October 10–11, 1973.

(5) Minutes of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 5th Meeting, October 10 and 11, 1973.

(6) Shafer, W. G., M. K. Hine, and B. M. Levy, "A Textbook of Oral Pathology," 3d Ed., W. B. Saunders Co., Philadelphia, p. 436, 1974.

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B. Categorization of Data

1. *Category I conditions under which active ingredients for the relief of toothache are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredient

Eugenol preparations (85 to 87 percent).

Eugenol preparations (85 to 87 percent). The Panel concludes that eugenol in a concentration of 85 to 87 percent in clove oil or any bland, fixed oil is safe and effective for use as an agent for the relief of toothache as specified in the dosage section below.

(1) *Safety.* Clinical use and marketing experience have confirmed that eugenol is safe for OTC use. Clove oil contains 85 to 87 percent eugenol; therefore, the Panel concludes that clove oil and eugenol essentially possess the same pharmacologic activity, and the term "eugenol" as used below indicates 85 to 87 percent eugenol in a bland, fixed oil or clove oil unless otherwise specified.

The Panel is fully aware that eugenol is sufficiently irritating to damage viable dental pulp and stresses that it should not be used in a tooth with intermittent pain (characteristic of pain caused by reversible pulp damage) (Ref. 2). The Panel concludes, however, that, with adequate labeling to indicate use only in throbbing, persistent pain (characteristic of irreversible pulp damage), eugenol is safe and effective as a toothache remedy for OTC use (Ref. 2).

In the dental literature there are reports dealing with the irritancy of eugenol preparations, especially tissue reactions to eugenol in periodontal dressings (Refs. 3, 4, and 5). In these studies none of the patients who showed irritation of the mucosa after exposure to eugenol preparations were subsequently examined by patch test for possible contact allergy, or for whether or not they had become hypersensitive to eugenol.

In one study, patients undergoing dental treatment in which eugenol-containing preparations were used, and who had reacted with swelling and redness, were patch-tested with eugenol (Ref. 6). Sixteen of 18 patients gave

clear-cut positive test reactions to eugenol. The history of these patients suggested that they had been sensitized to eugenol during dental treatment.

The amounts of eugenol used in dentistry are well below systemic toxicity levels. Aside from a few reports of hypersensitivity, the long history of use of eugenol as an anodyne attests to its safety for dental use when used on exposed dentin (Ref. 7). The use of eugenol is only recommended when there is persistent, throbbing pain. Intermittent pain may indicate that the pulp is still viable, and eugenol may compromise the pulp vitality in that case. A warning is recommended to describe when eugenol should not be used. (See part III. paragraph B.1. below—Category I Labeling.)

(2) *Effectiveness.* It is difficult to generalize about the effectiveness of a toothache preparation since the data on use of such preparations is difficult to interpret. Although data suggest that the effectiveness of self-medication is similar to that experienced with placebo drugs, eugenol's analgesic effects on dentin are recognized (Refs. 1 and 8). Well-controlled, published studies on the effectiveness of eugenol for the relief of toothache are not available. The Panel considered the opinions of acknowledged experts in endodontics who, however, did not agree with each other on the advisability of making eugenol available to the consumer as an OTC toothache remedy (Refs. 2 and 7), as well as published opinions of other experts that eugenol is a dental analgesic or has topical anesthetic effect (Refs. 1 and 9). Even though the opinions of the experts did not agree, the Panel feels that, based on all of the information evaluated by the Panel, eugenol can be generally recognized as effective as a dental analgesic and that it should be available to the consumer as an agent for the relief of toothache.

(3) *Dosage.* Adults and children 2 years of age and older: Place a cotton pledget moistened with 1 or 2 drops of 85 to 87 percent eugenol into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing active ingredients for the relief of toothache. (See part III. paragraph B.1. below—Category I Labeling.)

In addition, the Panel recommends the following warning for products containing eugenol:

"Do not use if you are allergic to eugenol."

References

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 209, 1977.

(2) Summary minutes of the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 5th meeting, October 10 and 11, 1973.

(3) Waerhaug, J., and H. Loe, "Tissue Reaction to Gingivectomy Pack," *Oral Surgery, Oral Medicine, and Oral Pathology,* 10:923–937, 1957.

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(5) Guglani, L. M., and E. F. Allen, "Connective Tissue Reaction to Implants of Periodontal Packs," *Journal of Periodontology,* 36:279–282, 1965.

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Category I Labeling

The Panel recommends the following Category I labeling for active ingredients for the relief of toothache:

a. *Indication.* "For the temporary relief of throbbing, persistent toothache due to a cavity until a dentist can be seen."

b. *Warnings*—(1) *For all agents for the relief of toothache.* (a) "Use only in teeth with persistent, throbbing pain."

(b) "Not to be used for a period exceeding 7 days."

(c) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(d) "Do not swallow."

(e) "Do not exceed recommended dosage."

(f) "Children under 12 years of age should be supervised in the use of this product."

(g) "A dentist must be seen as soon as possible whether or not the pain is relieved."

(h) "Toothaches and open cavities indicate serious problems which need prompt attention by a dentist."

(2) *For products containing eugenol.* "Do not use if you are allergic to eugenol."

c. *Directions.* Rinse the tooth with water to remove any food particles from the cavity. Moisten a cotton pledget with 1 or 2 drops of medication and place in the cavity for approximately 1 minute. Avoid touching tissues other than the tooth cavity. Apply the dose not more than four times daily or as directed by a dentist or physician. Children 2 to 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

2. *Category II conditions under which active ingredients for the relief of toothache are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC drug products for the relief of oral discomfort effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

Capsicum (for use in an open tooth cavity)
Menthol
Methyl salicylate

a. *Capsicum (for use in an open tooth cavity).* The Panel concludes that capsicum instilled into a tooth cavity is not safe for OTC use as an agent for the relief of toothache.

(1) *Safety.* Capsicum is an irritant dependent upon counterirritation for any therapeutic usefulness it may have in the relief of pain. Capsicum itself is very irritating to mucous membranes and even a minute quantity of the oleoresin will cause intense burning if it contacts the eyes or tender areas of the skin (Refs. 1 and 2). Capsicum is no longer described in "The United States Pharmacopeia" or "The National Formulary," and there are, therefore, no U.S. standards for its content of capsaicin, the active pungent constitutent. Commercial red peppers contain 0.1 to 1.0 percent of capsaicin (Ref. 3). "The British Pharmaceutical Codex" (BPC) specifies that capsicum contains about 0.5 to 0.9 percent capsaicin with the lower limit 0.5 percent; capsicum oleoresin (BPC) contains not less than 8 percent capsaicin weight/weight (w/w) (Ref. 3).

Toxicity of capsicum oleoresin is classified (with reservations) by Gosselin et al. (Ref. 1) as moderately toxic, the human lethal dose probably being 0.5 to 5 g/kg when ingested. It is very irritating to mucous membranes and if swallowed produces severe gastritis and diarrhea (Ref. 1).

In feeding studies a diet containing 0.014 percent capsaicin by weight was fed to rats for 28 and 56 days (Ref. 4). This diet produced ultrastructure

changes in duodenal absorptive cells. The amount of capsaicin ingested (approximately 1 mg/kg body weight daily) is approximately equivalent to the capsicum intake of people of rural Thailand. No histopathology studies of the effects of application of capsicum to skin or oral mucous membrane were found.

In general, irritating drugs instilled into a tooth cavity will injure a viable pulp, and OTC use of such agents by application into a tooth is unsafe.

(2) *Effectiveness.* No studies were found of the use of capsicum in dosage forms (toothache drops or toothache gum) to be instilled in the tooth cavity in order to relieve toothache pain.

(3) *Evaluation.* Use of a counterirritant for application to tissues that are irritated is irrational and unsafe. No clinical studies of the application of capsicum into a tooth cavity for relief of pain were found in the literature and none were submitted to the Panel.

References

(1) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, Section II, p. 145, 1976.

(2) Blacow, N. W., and A. Wade, "Martindale: The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, pp. 1235–1236, 1972.

(3) "British Pharmaceutical Codex 1973," The Pharmaceutical Press, London, pp. 72–73, 1973.

(4) Nopanitaya, W., "Effects of Capsaicin in Combination with Diets of Varying Protein Content on the Duodenal Absorptive Cells of the Rat," *American Journal of Digestive Diseases*, 19:439–448, 1974.

b. *Menthol.* The Panel concludes that menthol is not safe for OTC application as an agent for the relief of toothache.

(1) *Safety.* Although menthol does possess minimal anesthetic activity, if used in concentrations sufficient for anesthetic activity, it causes intense irritation with the possibility of local tissue destruction. The Panel concludes that menthol is not safe for instillation into a tooth as a local anesthetic.

Tainter, Throndson, and Moose (Ref. 1) applied a solution of 5 percent menthol in 95 percent ethanol to the oral mucous membranes of 36 humans. The menthol solution produced intense irritation when applied to oral mucosa and caused sloughs in 19 percent of the patients at a concentration of 5 percent menthol which is sufficient to produce local anesthesia. The 95 percent ethanol alone was also irritating and caused sloughs in 8 percent of the patients.

In young children, nasal drops containing menthol may cause spasm of the glottis, and cases of dangerous asphyxiation have been reported in infants following local application of menthol (Ref. 2).

The "United States Pharmacopoeia" (Ref. 3) categorizes menthol as a topical antipruritic and suggests that for external use it be applied topically to the skin as a 0.1- to 2.0-percent lotion or ointment. Concentrations of 0.1 to 2.0 percent are less than those found to have local anesthetic activity, and the "United States Pharmacopoeia" gives no indication for application of menthol to mucous membranes.

In a long-term study in experimental animals, 20 rabbits were treated with either 1-percent or 5-percent solutions of menthol in liquid petrolatum, sprayed daily to the nasal mucous membrances for 9 months (Ref. 4). Results showed that menthol produced sneezing and pain. The nose, bronchi, and lungs of all the rabbits showed some evidence of inflammatory changes, namely a purulent rhinosinobronchitis with numerous miliary abscesses and consolidation of lung tissue. The rabbits sprayed with a 5-percent menthol solution fared only slightly worse than those sprayed with the 1-percent solution. Liquid petrolatum as a control apparently also exerted a deleterious effect on the nasal mucosa of a rabbit when used for 9 months.

In general, irritating drugs instilled into a tooth cavity will injure a viable pulp; therefore, OTC use of menthol by application into a tooth is unsafe.

(2) *Effectiveness.* Nagira and Yao (Ref. 5) produced artificial toothaches in teeth of rabbits by electrical stimulation and tested the effectiveness of topical application of several agents in relieving the induced pain. They found phenol to be the best agent; clove oil, menthol, and eucalyptol were found to be weak anesthetics.

Yamashita (Ref. 6) studied the effectiveness of some local anesthetics dissolved in propylene glycol on the tympanum of guinea pigs. Dibucaine, cocaine, benzocaine, phenol, and menthol all exerted anesthetic actions and the intensities were in that order (menthol was the weakest).

In studies in humans, Adriani et al, (Ref. 7) found that a 3.5-percent menthol solution applied to the tip of the tongue produced anesthesia, with a mean latent period of 0.16 minutes and a mean duration of 1.5 minutes. This duration of action was the shortest of the 22 drugs to which local anesthetic activity was attributed.

Tainter, Throndson, and Moose (Ref. 1) applied a solution of 5 percent menthol in 95 percent ethanol to the oral mucous membranes of humans. The menthol solution produced complete anesthesia in 42 percent, partial anesthesia in 56 percent, and no anesthesia in 3 percent of 36 subjects. By comparison, 95 percent ethanol produced complete or partial anesthesia in 78 percent of the 156 persons tested, and aqueous placebo solutions proudced some degree of anesthesia in 43 percent of 576 tested. As noted above, the 5-percent menthol solution produced intense irritation when applied to oral mucosa and caused sloughs in 19 percent of the patients. They fond that a 5-percent concentration of menthol was necessary to produce local anesthesia (Ref. 1).

(3) *Evaluation.* Menthol possesses minimal local anesthetic activity, but if used in concentrations sufficient for this anesthetic activity, menthol causes intense irritation with the possibility of local tissue destruction. No claims can be made for menthol as a local anesthetic. Menthol should not, in any concentration, be instilled into a tooth cavity. Menthol may be included in preparations as an inactive ingredient (flavor) according to FDA regulations on flavors.

References

(1) Tainter, M. L., A.H. Throndson, and S. M. Moose, "Studies in Topical Anesthesia: II. Further Observations on the Efficacy of the More Common Local Anesthetics When Used on the Gums and Oral Mucosa, "*Journal of the American Dental Association and Dental Cosmetics*, 24:1480–1487, 1937.

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(6) Yamashita, S., "Studies of Tympanic Membrane Surface Anesthetics with Propylene Glycol as a Solvent," *Folia Pharmacologica Japonica*, 47:108–114, 1951.

(7) Adriani, J., et al., "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics*, 5:49–62, 1964.

c. *Methly salicylate.* The Panel concludes that methyl salicylate is not generally recognized as safe or effective for OTC application as an agent for the relief of toothache.

(1) *Safety.* Methyl salicylate causes irritation with the possibility of local tissue damage when applied to mucous

membranes (Refs. 1 and 2). In general, irritating drugs instilled into a tooth cavity will injure a viable pulp. Therefore, OTC use of methyl salicylate by application into a tooth cavity is unsafe. It is considered unsafe in conjunction with a tooth cavity even as a flavoring agent because of its irritating properties.

Because of the reputed systemic toxicity of methyl salicylate, the Panel recommends that any dentifrice or dental care agent containing this substance as a pharmaceutical aid (i.e., flavoring agent) be in conformity with all pertient regulations for its use as such.

(2) *Effectiveness.* Since there are no studies that methyl salicylate, when applied topically, provides an anesthetic effect, it apparently acts only as a counterirritant (Refs. 2 and 3).

(3) *Evaluation.* Methl salicylate is an irritant when applied topically, possible causing local tissue damage. It should not be instilled into a tooth cavity. The Panel concludes that there is no rational use of methyl salicylate as an agent to be instilled in a tooth cavity for the relief of toothache.

References

(1) Sollman, T., "A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology," 8th Ed., W. B. Saunders Co., Philadelphia, pp. 737 and 743–744, 1957.

(2) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., Williams and Wilkins, Baltimore, section II, p. 96, 1969.

(3) Traut, E. F., et al., "Topical Treatment in Rheumatic Disease," *Illinois Medical Journal,* 121:257–260, 1962.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of a product are unsupported by scientific data and, in some instances, by found theoretical reasoning. The Panel concludes that such labeling should be removed from the market.

The Panel considers the following examples of claims to be misleading and unsupported by scientific data:

"For quick temporary relief of pain and soreness due to minor irriation of teeth and gums." This type of toothache is not defined.

"For temporary relief of cavity toothache."

"Eases pain due to cavities fast."

"Quickly forms temporary filling."

"Fast relief from toothache due to cavities."

"Especially soothing after extractions or for minor gum boils."

"For rapid and effective relief of sore gums."

"For sore gums following tooth extractions."

"For use after tooth extraction."

"Hold in mouth as long and as frequently as necessary, then rinse." This is inconsistent with the directions for use proposed by the Panel.

"Temporary replacement for lost fillings."

"Gives quick relief that lasts for hours."

"For fast, temporary relief of minor mouth or gum soreness." The claim is too vague; it must be more specific.

"Subdues the throbbing ache of sore, swollen gums." The claim is too vague; gums may be infected or a deeper problem may exist.

The Panel considers that claims which imply a superiority in onset of action, such as "quicker," "more quickly," and "faster" are misleading.

The Panel considers the following terms to be vague and not definitive of the condition for which relief is sought: "sore spots," "anti-irritation," "comfortable adjustment," "helps comfortable adjustment," "stops pain," "soothes sore gums," "special," "unaccustomed use," "alleviates pain."

The following claims are for conditions that require advice of a dentist: "gum boils," "gum or gingival inflammation," and "abscesses."

For products containing a counterirritant: "Relieves irritation."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I except as noted for specific pharmacotherapeutic groups.

Category III Active Ingredients

Benzocaine
Benzyl alcohol (1 to 3 percent)
Butacaine sulfate
Capsicum (as a counterirritant)
Cresote
Cresol
Eugenol (1 to 84 percent)
Phenol preparations (phenol and phenolate sodium)
Thymol preparations (thymol and thymol iodide)

a. *Benzocaine.* The Panel concludes that there are insufficient data available to establish the effectiveness of 2 to 20 percent benzocaine as an OTC agent for the relief of toothache.

(1) *Safety.* The Panel has discussed the safety of benzocaine elsewhere in this document. (See part IV. paragraph B.1.a.(1) below—Safety.)

(2) *Effectiveness.* Benzocaine is classified by the Panel as an effective oral mucosal analgesic. (See part IV. paragraph B.1.a.(2) below—Effectiveness.) However, there are insufficient data to establish effectiveness of benzocaine after application into a tooth cavity, as an agent for the relief of toothache, at the 2- to 20-percent concentrations.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Place a cotton pledget moistened with 2 to 20 percent benzocaine into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for active ingredients for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warning for products containing benzocaine:

"Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to establish the effectiveness of benzocaine as an agent for the relief of toothache. Data to demonstrate effectiveness as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III, paragraph C. below—Data Required for Evaluation.)

b. *Benzyl alcohol.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of benzyl alcohol at a concentration of 1 to 3 percent for OTC use as an agent for the relief of toothache.

(1) *Safety.* There are insufficient data to establish the safety of 1 to 3 percent benzyl alcohol for use as an agent for the relief of toothache.

In general, irritating drugs instilled into a tooth cavity will injure a viable pulp, and OTC use of such agents by application into a tooth is unsafe. An additional problem is that application of benzyl alcohol into a tooth cavity may increase permeability of the dentin. Application of benzyl alcohol into the tooth may, therefore, increase any adverse effects of other drugs applied concomitantly (Ref. 1). Benzyl alcohol in 100 percent concentration is irritating to tissue; injected subcutaneously or intramuscularly, the drug produces local necrosis (Refs. 2, 3, and 4).

When injected in the area of branches of the facial nerve in cats, 10 percent benzyl alcohol in almond oil produced

prolonged motor nerve block, and it caused degeneration of nerve fibers in the injected area (Ref. 5). Tested in the same way, 5 percent benzyl alcohol in almond oil produced only transient weakness of the appropriate muscles, but even this lower concentration caused degeneration of a significant number of nerve fibers. Almond oil itself has no observable effect on the nerve fibers.

Aqueous solutions in concentrations from 1 to 3 percent of benzyl alcohol may produce variable degrees of irritation to soft tissues. Aqueous preparations containing greater than 3 percent benzyl alcohol are likely to contain undissolved benzyl alcohol. The studies cited above show that undissolved benzyl alcohol is a potent irritant. Therefore, preparations greater than 3 percent may be unsafe for instillation into a tooth cavity for the relief of toothache or for application to oral soft tissues.

Because animal studies suggest that ingestion of benzyl alcohol at a rate of 1 mL/kg may be fatal (Ref. 1), and since package sizes that will provide more than 30 mL of a 2-percent solution of 60 mL of a 1-percent solution are unnecessary and may be a potential risk for accidental ingestion by young children, the Panel recommends that package size be limited to that containing a total of 0.6 mL of benzyl alcohol.

(2) *Effectiveness.* The Panel has discussed the effectiveness of benzyl alcohol elsehwere in this document. (See part IV. paragraph B.3.a.(2) below—Effectiveness.) Benzyl alcohol does have local anesthetic activity, but studies of effectivness by application into a tooth cavity for the relief of toothache are not available.

Since benzyl alcohol solutions stored in soft glass containers have been shown to increase in pH and drecrease in anesthetic ativity, the Panel believes there may be stability problems with blezyl alcohol solutions in some dosage forms or in some types of packaging. Therefore, the stability of benzyl alcohol in the particular dosage form and packaging intended for marketing should be established (Ref. 6).

(3) *Proposed dosage,* Adults and children 2 years of age and older: Place a cotton pledget moistened with 1- to 3-percent benzyl alcohol into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for active ingredients for the relief of toothache, (See part III. paragraph B.1. above—Category I Labeling).

In addition, products containing benzyl alcohol should contain no more than a total of 0.6 mL (30 mL of a 2-percent solution or 60 mL of a 1-percent solution) of benzyl alcohol in a container capable of maintaining stability of the product.

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to establish the safety and effectiveness of 1 to 3 benzyl alcohol as an agent for the relief of toothache. Data to demonstrate safety and effectiveness as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

Benzyl alcohol does possess local anesthetic activity, but the concentrations (in aqueous and nonaqueous solvents) needed to provide relief of pain arising from the tooth pulp have not been established. Benzyl alcohol at a concentration of 100 percent is a potent irritant, and the maximal safe concentrations (in aqueous and nonaqueous solvents) of solutions for application to oral mucosa have not been established. Since only 1 g of benzyl alcohol is soluble in about 25 to 30 mL of water, aqueous preparations containing more than 3 to 4 percent benzyl alcohol may produce irritation as a result of some undissolved benzyl alcohol.

References

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c. *Butacaine sulfate.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 4 percent butacaine sulfate as an agent for the relief of toothache.

(1) *Safety.* Butacaine sulfate is classified by the Panel as a safe oral mucosal analgesic. (See part IV, paragraph B.1.c. (1) below—Safety.) However, the Panel concludes that there are insufficient data to establish the safety of 4 percent butacaine sulfate as an agent for the relief of toothache.

(2) *Effectiveness.* Butacaine sulfate is classified by the Panel as an effective oral mucosal analgesic. (See part IV. paragraph B.1.c. (2) below—Effectiveness.) However, there are insufficient data to establish effectiveness of 4 percent butacaine sulfate after application into a tooth cavity as an agent for the relief of toothache.

(3) *Proposed dosage.* Adults and children 12 years of age and older: Place a cotton pledget moistened with 4 percent butacaine sulfate into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for active ingredients for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warnings for products containing butacaine sulfate:

(a) "Do not use in children under 12 years of age unless recommended by a dentist or physician."

(b) "Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 4 percent butacaine sulfate as an agent for the relief of toothache. Data to demonstrate the safety and effectiveness of butacaine sulfate as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

(d) *Capsicum (as a counterirritant.* The Panel concludes that there are insufficient data available to permit final classification of the effectiveness of capsicum equivalent to 0.01 to 0.02 percent of capsaicin for OTC use as an agent for the relief of toothache as a counterirritant on intact (normal) oral mucosa as specified in the proposed dosage section discussed below. Capsicum is safe for application to normal oral mucous membranes, but is considered unsafe for application into a tooth cavity or for use on irritated oral

mucosa. (See part III. paragraph B.2.a. above—Capsicum.)

(1) *Safety.* Clinical use and marketing experience have confirmed that capsicum equivalent to 0.02 percent of capsaicin is safe for OTC use on normal oral mucosa.

As used in drug products intended for application to skin or mucous membrane, the desired pharmacologic effect of dilutions of capsicum and capsicum oleoresin is a mild local irritation. Safety evaluations are related to estimation of the degree of local irritation produced by acute use of a counterirritant in a suitable dosage form and chronic irritation due to prolonged application which could theoretically have some adverse effects, but long-term use would be excluded by proper labeling. Package size should be limited to a maximum amount for eight applications so as to discourage prolonged use.

Two evaluations of dental poultices containing capsicum contribute some limited information on irritant effects, or lack thereof, of capsicum or oral mucosa. In 1936 a dental poultice stated to contain 2.3 percent capsicum, and 6 other ingredients (including aconite, which is an irritant) was evaluated by the Council on Dental Therapeutics of the American Dental Association (Ref. 1). Tests by a pharmacologist in which three subjects applied the test poultice to the buccal cavity on one side and a poultice composed of hops on the other side showed no burning or erythema at the site of application on either side. The capsicum poultice produced very mild burning on the tongue.

The poultice was reformulated and again submitted to the Council (Ref. 2). The revised formula contained 2.3 percent capsicum with 3 percent benzocaine and 4 ingredients stated by the reference to be inactive. The report states, "Laboratory and clinical studies indicate that this product will produce no harmful local effects." The report summarizes four clinical studies, only one of which mentions tissue irritation or lack thereof. In this study, reddening of the oral mucosa was evaluated after 1-hour contact with the poultice and with a control poultice. In 30 subjects the medicated poultice produced hyperemia to the same or less degree than the control poultice; in 20 subjects there was more hyperemia from the medicated poultice than from the control poultice. It must be noted, however, that the literature is conflicting in regard to whether or not capsicum is a rubefacient, and hyperemia may not be a valid measure of irritant effect (Refs. 3, 4, and 5). In addition, a local anesthetic may inhibit the local vasodilation response to a rubefacient drug (Ref. 6). (See part III. paragraph B.2.a. (1) above—Safety.)

(2) *Effectiveness.* As an active ingredient of dental poultices, capsicum is claimed to provide relief of toothache (as a counterirritant) when the poultice is applied to the gum.

A published Council on Dental Therapeutics report (Ref. 2) on the effectiveness of a capsicum-containing poultice includes the only four clincial studies that could be found. The poultice contained 2.3 percent capsicum, 3 percent benzocaine, and 4 other ingredients, including hops, labeled as inactive ingredients. In the first study, which was sponsored by the manufacturer, participating dentists alternately gave the test poultice or a hops poultice to patients suffering mild pain. The patients were asked to report (on a card) the rapidity and degree of pain relief afforded by the poultices. The company reported that the medicated poultice showed measurable superiority over the placebo, but the company also noted that the results of this first study were not particularly conclusive. The Council itself conducted a similar study, except that efforts were made to prevent the dentist and the patient from identifying which poultice was the active one. Results indicated no particular superiority of the capsicum-benzocaine poultice over the placebo. There was a very high placebo response. In a third study, a placebo "pill" was compared with the test poultice. The results were more favorable for the poultice than for the pill, but of course the control drug was an inadequate control. The fourth study was a double-blind, controlled study conducted by the Council's referee. The subjects were dental students. The medicated poultice was placed on one side of the maxilla in the bicuspid area, and the placebo was placed on the other side. After 1 hour of application the effects were evaluated, including taste (burning and bitter), hyperemia of the tissues, and tissue sensitivity. Only in taste was there a statistically significant difference between the placebo and test poultices. This fourth study did not attempt to evaluate relief of clinical pain. Measuring "tissue sensitivity" would evaluate the effects of the benzocaine component, but not the effects of capsicum.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Apply 0.01 to 0.02 percent capsicum in a dental poultice dosage form.

(4) *Labeling.* The Panel recommends the Category I labeling for agents for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warnings for products containing capsicum:

(a) "Do not install in tooth cavity."

(b) "Do not apply to irritated oral soft tissue. Use only on healthy tissue."

(c) "To avoid danger of choking, do not leave a poultice in the mouth during periods of sleep."

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the effectiveness of 0.01 to 0.02 percent capsicum as an agent for the relief of toothache (counterirritant). Data to demonstrate effectiveness as an agent for the relief of toothache as a counterirritant will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

Although capsicum appears to be a safe drug when it is used occasionally in low concentrations for topical application to oral mucous membranes, there are presently no data to indicate what concentration of capsicum is needed for effectiveness when applied in this way as a counterirritant.

If effective, capsicum will only relieve pain symptoms and may, therefore, disguise the true disease process. For this reason and because chronic irritation is unsafe, products containing capsicum should be labeled to indicate only temporary use.

Effectiveness should be established by two well-controlled clinical studies in which a capsicum dosage form affords significantly ($P < 0.05$) more pain relief than the appropriate placebo. Accepted indices of analgesic effectiveness, such as pain intensity differences (PID), total pain relief (TOTPAR), or numbers of patients with pain reduction greater than 50 percent, could be used to evaluate effectiveness of capsicum in relieving clinical pain originating from oral tissues. Two years should be allowed for such studies.

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e. *Creosote.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 0.25 to 1.5 percent creosote as an agent for the relief of toothache.

(1) *Safety.* Creosote, beechwod creosote, is obtained by the distillation of wood tar and is composed of a large number of phenolic compounds, the greater quantities of which are guaiacol (2-methoxyphenol) and creosol or methylguaiacol (2-methoxy,4-methylphenol) (Ref. 1). These phenols have toxicities similar to, but less than, that of phenol (Ref. 2). Like phenol, creosote and guaiacol are absorbed through the skin and mucous membranes (Refs. 2, 3, and 4). Phenols are protoplasmic poisons (Ref. 5). Although stated to be somewhat less toxic than phenols, creosote and its two major constitutents, creosol and guaiacol, are irritant corrosive fluids capable of damaging tooth pulp and destroying nerves (Refs. 2 and 6). As with phenol, the maximum safe concentration of creosote for application to an open tooth cavity has not been established. The depth of the tooth cavity, and therefore its proximity to the pulp, is a major factor in the safety of placing any kind of medication into the tooth, since these medications may cause pulpal irritation, resulting in irreversible damage.

(2) *Effectiveness.* Creosote is similar to phenol in that when it is applied locally it paralyzes sensory nerves and is anesthetic as well as being irritating and germicidal (Ref. 6). Application of a droplet of full-strenth creosote to the cavity of a carious tooth usually relieves toothache temporarily (Ref. 3). However, no data were presented or found in the literature on effectiveness of solutions of creosote in the treatment of toothache, and irritant properties of creosote preclude its OTC use in full-strength.

(3) *Proposed dosage.* Adults and children 6 years of age and older: Place a cotton pledget moistened with 0.25 to 1.5 percent creosote into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for active ingredients for the relief of toothache. (See Part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warning for products containing creosote:

"Do not use in children under 6 years of age unless recommended by a dentist or physician."

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 0.25 to 1.5 percent creosote in the tooth cavity for the relief of toothache. Data to demonstrate safety and effectiveness of creosote as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—data Required for Evaluation.) These studies should be completed in a 30-month period.

References

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(6) Osol, A., et al., "The Dispensatory of the United States," 24th Ed., J. B. Lippincott Co., Philadelphia, p. 338, 1947.

f. *Cresol.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 0.25 to 1.0 percent cresol as an OTC agent for the relief of toothache.

(1) *Safety.* Cresol, a mixture of 2-, 3-, 4-methylphenols is obtained by fractional distillation of coal tar or petroleum (Refs. 1 and 2). Cresol is a protoplasmic poison resembling phenol in its effects although it may be slightly more corrosive than phenol, and its systemic effects may be slightly milder because of slower absorption (Refs. 3 and 4). In an in vitro test, 0.25 percent cresol, 0.54 percent phenol, 0.3 percent *m*-cresol, and 1.2 percent benzyl alcohol produced total hemolysis of erythrocytes (Ref. 5). In a study of carcinogenic activity of phenol and related compounds on mouse skin, each of the three cresols was reported to have the same order of "promoting" activity as phenol (Ref. 6).

On the skin, cresol produces erythema, burning, and numbness (Ref. 2). If ingested, cresol causes a severe burning sensation in the mouth and upper abdomen, dysphagia (difficulty in swallowing), vomiting, and diarrhea (Ref. 2). Chronic poisoning (by ingestion or by percutaneous absorption) may produce widely varied reactions such as gastrointestinal disturbances, central nervous system dysfunctions, skin eruptions, jaundice, oliguria, and uremia (Ref. 7). At least one death has been reported from topical application of cresol to a large area of the body surface of a child (Ref. 8). Irritation of periapical tissues may occur if cresol is used in root canal therapy (Ref. 1).

(2) *Effectiveness.* Early studies in experimental animals and man suggest that cresol solutions have some local anesthetic activity (Refs. 9 through 12). Gurney (Ref. 13) reports that cresols have been used as mild pulpal analgesics and that when applied under proper conditions they exhibit a demonstrable analgesia. He notes that the analgesia may be easily seen with application of cresol to irritated pulps of primary teeth but that analgesia is very difficult to demonstrate with permanent teeth. Gurney's paper did not include clinical studies.

The Panel conducted a thorough search of the scientific literature for clinical studies of cresol as a local anesthetic for use on soft oral tissue or for the relief of toothache. Such studies were not found. One submission included one unpublished clinical study of the obtundent qualities of a product containing cresol and boric acid (Ref. 14). This clinical study apparently included more than 120 patients, but it was uncontrolled, not well-documented, and evaluations were subjective.

(3) *Proposed dosage.* Adults and children 6 years of age and older: Place a cotton pledget moistened with 0.25 to 1.0 percent cresol in aqueous solution into the tooth cavity for approximately 1 minute. The total amount to be applied in a 24-hour period should not exceed 400 mg for adults or 200 mg for children 6 to 12 years of age.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing active ingredients for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warning for products containing cresol:

"Do not use in children under 6 years of age unless recommended by a dentist or physician."

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of 0.25 to 1.0 percent cresol in the tooth cavity for the relief of toothache. Data to demonstrate safety and effectiveness of

cresol as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 209, 1977.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 355, 1973.

(3) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 63, 1977.

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(6) Boutwell, R. K., and D. K. Bosch, "The Tumor-promoting Action of Phenol and Related Compounds for Mouse Skin," *Cancer Research*, 19:413–424, 1959.

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(9) Ikebe, S., "Experimental Study on Surface Anesthesia of the Outer Ear Passage in Guinea Pigs," (abstract), *Chemical Abstracts*, 29:2599, 1935.

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(11) Kasuga, E., "Percutaneous Anesthesia," (abstract), *Chemical Abstracts*, 34:7428, 1940.

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(14) OTC Volume 080013.

g. *Eugenol (1 to 84 percent).* The Panel concludes that 1 to 84 percent eugenol is safe but that there are insufficient data available to permit final classification of its effectiveness for use as an OTC agent for the relief of toothache.

(1) *Safety.* The Panel has discussed the safety of eugenol elsewhere in this document. (See part III. paragraph B.1.(1) above—Safety.)

(2) *Effectivenes.* The Panel concludes that eugenol in concentrations of 1 to 84 percent may be effective as an agent for the relief of toothache since it is recognized as effective at a concentration of 85 to 87 percent. (See part III. paragraph B.1.(2) above—Effectiveness.) However, there are insufficient data to establish the effectiveness of eugenol in lower concentrations (Refs. 1 and 2). The Panel, therefore, recommends that studies be conducted within this dosage range.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Place a cotton pledget moistened with 1 to 84 percent eugenol into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing active ingredients for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

In addition, the Panel recommends the following warning for products containing eugenol:

"Do not use if you are allergic to eugenol."

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the effectiveness of 1 to 84 percent eugenol in the tooth cavity for the relief of toothache. Data to demonstrate the effectiveness of 1 to 84 percent eugenol as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) OTC Volume 080003.

(2) OTC Volume 080081.

h. *Phenol.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of phenol in concentrations up to 1.5 percent for OTC use as an agent for the relief of toothache as specified in the proposed dosage section below.

(1) *Safety.* The Panel concludes that phenol in concentrations up to 1.5 percent in aqueous solution is safe for application to oral mucous membranes, but the maximum safe concentration for application to an open tooth cavity has not been established. The depth of the tooth cavity and therefore its proximity to the pulp is a major factor in the safety of placing any kind of medication into the tooth because these medications may cause pulpal irritation resulting in irreversible damage.

The opinions of two acknowledged research experts in endodontics cite phenol's capacity to damage odontoblasts by increasing the permeability of dentinal tubules (Refs. 1 and 2). They further state that phenol, as a protoplasmic poison, may stop pain, but its potential to produce pulp damage warrants its elimination from toothache preparations. Nevertheless, the Panel had no convincing evidence that phenol in concentrations up to 1.5 percent was unsafe and therefore placed it in Category III. (See part IV. paragraph B.1.c.(1) below—Safety.)

(2) *Effectiveness.* The local anesthetic activity of low concentrations of phenol is due to its ability to block nerve conduction, but this action is limited. High concentrations demyelinate or otherwise destroy many types of nerve endings (Refs. 3 and 4).

The effectiveness of phenol as an agent for the relief of toothache has never been demonstrated. Originally, phenol was used in dentistry for so-called "cavity sterilization"; however, because high concentrations of phenol have been shown to do more harm than good by increasing the permeability of dentin, its use is no longer advocated (Refs. 1 and 2). (See part IV. paragraph B.1.c.(2) below—Effectiveness.)

(3) *Proposed dosage.* Adults and children 2 years of age and older: Place a cotton pledget moistened with 1.5 percent phenol in aqueous solution into the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing active ingredients for the relief ot toothache. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the safety and effectiveness of phenol as an agent for the relief of toothache. Data to demonstrate safety and effectiveness of phenol as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

References

(1) Ellison, R., presentation to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 5th Meeting, October 10–11, 1973.

(2) Bender, I. B., presentation to the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products, 14th Meeting, October 16–17, 1974. (See Appendix II of the minutes of the 15th Meeting, December 4–5, 1974).

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i. *Thymol preparations (thymol and thymol iodide).* The Panel concludes that thymol preparations in concentrations up to 20 percent are safe

but that there are insufficient data available to permit final classification of their effectiveness for use as OTC agents for the relief of toothache as specified in the proposed dosage section below.

(1) *Safety.* The acute toxicity of thymol in a solution of propylene glycol was determined by oral administration to experimental animals (Ref. 1). Groups of 10 young adult Osborne-Mendel rats, evenly divided by sex, were fasted for approximately 18 hours and given the test material. The LD_{50} was 0.98 g/kg with a death time ranging from 4 hours to 5 days. The toxic signs with high doses consisted of depression, ataxia (failure of muscle coordination), and coma.

The minimum oral lethal dose of thymol has been reported to be 800 mg/kg in the mouse, 750 to 1,000 mg/kg in the rabbit, and 250 mg/kg in the cat (Ref. 2).

Thymol is considered to be less toxic than phenol. In humans fats and alcohol increase absorption and aggravate the toxic symptoms (Ref. 3). Thymol is completely absorbed from the intestine. It is excreted in the urine as the sulfate and glucuronide together with some thymol-quinone. About half of a dose is destroyed in the body. Thymol is an irritant to the kidneys (Ref. 3).

There are no apparent studies on thymol iodide; however, when thymol iodide was fed to rats for 5 weeks in a study designed to demonstrate iodide availability, there was considerable uptake of iodide by the thyroid (Ref. 4).

Boutwell and Bosch (Ref. 5) studied over 50 compounds related to phenol for their ability to promote the development of skin following a single initiating dose of dimethylbenzanthracene. One of the compounds tested (2-isopropyl-4-methylphenol) is closely related to thymol. When dissolved in 16 percent benzene and applied weekly for 12 weeks to mice, 19 percent developed skin tumors and 6 percent (1 and 16 mice) developed a carcinoma.

"The United States Dispensatory" (Ref. 6) states that thymol can cause nausea, vomiting, albuminuria, headache, tinnitus, dizziness, muscular weakness, a thready pulse, slow respiration, and a full in body temperature. It further states that the heart is depressed by "therapeutic" doses. Thymol used systemically in the treatment of mycosis has been given as divided oral doses consisting of 1 to 2 g daily being administered in courses of 2 of each 3 days. It has also been used as an intestinal antiseptic, in doses up to 120 mg.

Gleason et al. (Ref. 7) state that the toxicity of thymol is believed to lie on the borderline between toxicity classes 3 and 4 (moderately toxic and very toxic).

Thymol is less toxic than phenol, and larger doses may be taken (Ref. 3). It generally irritates tissues and given orally irritates the gastric mucosa. Rashes from thymol are not uncommon (Ref. 3). It was formerly used for the treatment of hookworm infestations, but it had to be used in such large doses that there was danger of serious, even fatal, poisoning. Oral doses stimulate peristalsis and may cause diarrheal stood (Ref. 6).

Thymol should not be given by mouth to persons with gastrointestinal disorders or impaired kidney function. It should be given with care to patients with heart disease (Ref. 3). However, the amounts used topically in the oral cavity are insufficient to cause problems for these individuals.

(2) *Effectiveness.* Thymol is used chiefly as a deodorant in antiseptic mouthwashes and gargles. Mixed with phenol and camphor, thymol is used in dentistry to prepare cavities before filling, and mixed with zinc oxide it forms a protective cap for the dentine (Ref. 3).

There are reports of use of thymol or thymol iodide in products for the relief of toothache, but there are insufficient data to establish effectiveness (Refs. 1 through 7). Since eugenol and thymol are chemically similar, the possibility of effectiveness as an agent for the relief of toothache is suggested and has frequently, in fact, been associated with professional use for this purpose (Ref. 3).

(3) *Proposed dosage.* adults and children 2 years of age and older: Place a cotton pledget moistened with a maximum of 20 percent thymol or thymol iodide in the tooth cavity for approximately 1 minute not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for active ingredients for the relief of toothache. (See part III. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that there is insufficient information to establish the effectiveness of thymol preparations as agents for the relief of toothache. Data to demonstrate effectiveness as an agent for the relief of toothache will be required in accordance with the guidelines set forth below. (See part III. paragraph C. below—Data Required for Evaluation.)

References

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(4) Mittler, S., and G. H. Benham, "Nutritional Availability of Iodine from Several Insoluble Iodine Compounds," *Journal of Nutrition,* 53:53–58, 1954.

(5) Boutwell, R. K., and D. K. Bosch, "The Tumor-promoting Action of Phenol and Related Compounds for Mouse Skin," *Cancer Research,* 19:413–424, 1959.

(6) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1190, 1973.

(7) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., Williams and Wilkins, Baltimore, p. 143, 1969.

Category III Labeling

None.

C. Data Required for Evaluation

The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *Principles in the design of an experimental protocol for testing agents for the relief of toothache*—a. *General principles.* As far as the Panel could determine, no acceptable studies had been published which prove effectiveness of an agent for the relief of toothache. The recommendation of eugenol (85 to 87 percent) in oil of cloves for Category I was made on the basis of a long history of use by dental practitioners. The Panel recommends that Category III agents for the relief of toothache be tested using the following protocol. Also, the Panel would like to encourage industry to study eugenol and oil of cloves using the same protocol in order to determine the performance of such standards. Such data would be useful in either verifying the Panel's conclusions or for future amendment of the monograph.

b. *Selection of patients.* Patients are screened when they enter the program to determine whether they have severe, throbbing, and persistent toothache which is described as intolerable. Subjects should be restricted to adults 20 to 50 years of age not taking central nervous system medications or having physical illness.

c. *Study method.* Three investigators at separate institutions, preferably academic institutions, should perform these studies. The general plan should be a sequential analysis as described in

several publications (Refs. 1, 2, and 3). The medication and placebo should be coded with random numbers and supplied in pairs.

Patient A receives one of the pair of medications. The tooth cavity is gently rinsed with warm water and the medication is placed in the cavity on a piece of cotton. The cotton is removed after 5 minutes. In the case where the agent for the relief of toothache is a gel, the gel is placed directly in the tooth cavity without cotton and allowed to leach out. The investigator then asks the patient to determine whether the pain is now tolerable. If the pain is still intolerable, no relief is noted for patient A and the dentist performs his or her normal procedure on the tooth according to diagnosis. To determine the duration of tolerable pain the same inquiry is conducted every 10 minutes for 90 minutes or until the subject says the pain has become intolerable again. At that time, the dentist performs his or her normal procedure on the tooth according to diagnosis.

Patient B receives the second medication of the pair, and the same procedure is followed. The code is broken, and a point is plotted on the sequential chart as follows:

(1) The active vs. placebo no point plotted: no relief obtained with either agent, or both agents provided relief but relief did not last at least 20 minutes more for one agent than for the orther.

(2) Active better than placebo: pain becomes tolerable in the active-agent subject and remains so for 20 minutes more than for the placebo subject.

(3) Placebo better than active: Pain becomes tolerable in the placebo subject and remains so for 20 minutes more than in the active-agent subject.

d. *Interpretation of data.* Pairs of patients are repeated whenever they become available until statistical significance (p less 0.05) is reached on the sequential analysis chart. No attempt is made to pair patients other than on the basis of time of arrival. Blinding of the investigator and the subject may be difficult with aromatic substances such as eugenol and thymol. It is recommended that a third bottle be supplied with each pair of test agents. This bottle should contain 85 to 87 percent eugenol or oil of cloves. It should be opened first before opening any coded medication. Just before the test substance is applied to the tooth a small amount of eugenol is placed on the tongue. This procedure may, to some degree, mask the effect of taste and odor. In addition, placebo and test substance should resemble each other in color and viscosity.

Also, the safety of benzyl alcohol, butacaine, creosote, cresol, and phenol as agents for the relief of toothache should be demonstrated by well-designed studies in the tooth cavities of humans under conditions of proposed use.

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2. *General principles in the design of an experimental protocol for testing counterirritants as agents for the relief of toothache.* Currently there are no generally accepted protocols for testing the effectiveness of counterirritant ingredients. The Panel recommends that the industry and FDA consider and develop mutually acceptable methodology.

The only counterirritants considered by the Panel were intended for application to the gum. Factors involved in the testing of agents for the relief of toothache, as discussed above, would be applicable as well to testing counterirritants and would provide a useful basis for comparison. (See part III. paragraph C.1. above—General principles in the design of an experimental protocol for testing agents for the relief of toothache.) This approach has not been previously used in testing counterirritants, but is pertinent to such ingredients which may claim to relieve toothache by the application of a poultice. (See part III. paragraph B.3.d. above—Capsicum.)

IV. Oral Mucosal Analgesics (Topical Anesthetics)

A. General Discussion

Oral mucosal analgesics are surface or topical anesthetics, and they are used as dental care agents by surface application to provide temporary relief of oral discomfort. Some injectable local anesthetics have surface anesthetic properties when applied topically in ointment, gel, or other topical dosage forms. Included in this category are lidocaine and butyl-derivatives of procaine, such as tetracaine and butacaine (Ref. 1). Benzocaine (ethylaminobenzoate) is very commonly used as a surface anesthetic; slow absorption makes it safe for use on wounds and mucous membranes (Ref. 2). Benzocaine is chemically related to procaine, but because of its lack of water solubility it is not useful as an injectable local anesthetic (Ref. 1).

The most commonly used surface anesthetics for OTC dental use are benzocaine and butacaine; for dental office use, lidocaine and tetracaine are the most commonly used (Ref. 3). Another drug, dyclonine is chemically dissimilar to commonly used surface anesthetics and may be used in dental offices for patients allergic to procaine, benzocaine, or chemically similar drugs (Ref. 1). In addition, combinations of surface anesthetics are often used in dental offices.

Various aromatic principles and alcohols also have modest to intense surface anesthetic effects. Tainter (Ref. 4) found that phenol, benzyl alcohol, menthol, and chlorobutanol have topical anesthetic activity. However, he claimed that phenol (used at 5 percent) was too caustic to be useful, while chlorobutanol at 10 percent and menthol at 5 or 10 percent were irritating. Studies by Adriani et al. (Ref. 5) indicated that classical injectable local anesthetics that are highly toxic (tetracaine, cocaine, dibucaine, and butacaine) were also highly effective surface anesthetics, while aromatic compounds (benzyl alcohol and menthol) were not nearly as effective.

1. *Adverse effects.* Adverse effects from surface anesthetics are due to overdosage, local irritation, or allergy.

a. *Overdosage.* Most anesthetic bases are rapidly absorbed when applied on the mucosal tissues (Ref. 6). Therefore, the maximum permissible dose (MPD) by intravenous injection should not be exceeded when applying the drug to the oral mucosa. Tetracaine and dibucaine have low MPD's because of high toxicity on intravenous administration (Ref. 4). These drugs are absorbed rapidly from the oral mucosa. When used as an agent to be applied topically to the oral mucosa, the dosage which is absorbed may exceed a safe dose and may cause systemic toxicity including seizures (Ref. 5). Their use should be closely supervised by a dentist.

Benzocaine appears to be an ideal surface anesthetic because, even when applied at high concentrations, overdosage is not likely to occur. Furthermore, it does not irritate the tissues at concentrations used in OTC products. Butacaine, although frequently used in dental ointments, has toxicity about equal to tetracaine. This toxicity level caused the Panel some concern, but based on safety studies provided during Panel deliberations, a long history of safe use, and a lack of adverse reaction reports, the Panel recommends butacaine for Category I classification (Refs. 1, 2, and 3).

b. *Local irritation.* As noted above, local irritation from surface application occurs only with a higher concentration of aromatic compounds or alcohols. The Panel considered local irritation as a a limiting factor in determining maximum safe concentrations of these agents.

c. *Allergy.* Although allergy to local anesthetics is considered rare, it does occur, especially with drugs related chemically to procaine. Benzocaine and butacaine are both in this category. Patients who are allergic to "caine" anesthetics should be warned on the package labeling, "Do not use this product if you are allergic to (name of local anesthetics) or other 'caine' anesthetics." These patients should use topical anesthetics only under the supervision of a dentist or physician. Since allergies to local anesthetics are quite rare, the target population for a new nonallergenic anesthetic would be extremely small; thus, there may not be an incentive to develop an OTC anesthetic which has no cross-reactivity with currently used local anesthetics.

Dental indications for use of topical anesthetics for the relief of oral discomfort include temporary relief of pain due to minor irritation or injury of soft tissues of the mouth, temporary relief of pain due to minor dental procedures, temporary relief of pain due to minor irritation of soft tissues caused by dentures or orthodontic appliances, temporary relief of pain due to canker sores when the condition has been previously diagnosed by a dentist or physician, and temporary relief of sore gums of infants and children due to teething.

2. *Carcinogenicity of phenol and phenolic compounds.* The Panel was concerned with reports of the carcinogenic and cocarcinogenic potential of phenol and phenolic substances, especially the studies of Boutwell and his coworkers and other groups (Refs. 7 through 13). Therefore, in addition to thorough study by the Panel, two experts were invited to make presentations to the Panel (Refs. 14 and 15).

These presentations were especially helpful, since they presented current views of earlier studies. The key point was that the cocarcinogenic effect of phenolic compounds is reversible and that low concentrations by themselves are not carcinogenic. Thus, if concentrations such as those recommended for mouth rinses or other OTC preparations are sufficiently low and the period of their use is restricted, there is no evidence that such use induces oral carcinoma. The Panel accepted 1.5 percent phenol in aqueous solution or in 20 percent ethyl alcohol as a dental rinse or in 70 percent ethyl alcohol for direct application to gums as the maximum generally recognized as safe (GRAS) concentration with a limit of 7 days use for any course of therapy, unless treatment is under the supervision of a dentist or physician. (See part IV. paragraph B.1.c. below—Phenol.) Under these conditions phenol and similar compounds are considered GRAS.

Cresol, a phenolic compound, is recommended for Category III requiring effectiveness studies with the safe concentration ranging from 0.25 to 1 percent. The same time limitation of 7 days is recommended for cresol and phenol labeling. (See part IV. paragraph B.3.b. below—Cresol.)

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B. Categorization of Data

1. *Category I conditions under which oral mucosal analgesic active ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredients.

Benzocaine
Butacaine sulfate
Phenol preparations (phenol and phenolate sodium)

a. *Benzocaine.* The Panel concludes that 5 to 20 percent benzocaine base in appropriate vehicles is safe and effective for OTC use as an oral mucosal analgesic for the relief of oral discomfort as specified in the dosage section discussed below. Appropriate vehicles are polyethylene glycol or propylene glycol water-soluble bases, ointment bases, ethyl alcohol up to 70 percent (maximum dosage 1.0 mL), and denture adhesive powders or creams.

The local anesthetic benzocaine (ethyl aminobenzoate) is the ethyl ester of para-aminobenzoic acid (Refs. 1 through 4). It has also been named anesthesin, orthesin, and parathesin. It occurs as an odorless, white, crystalline solid, which is very slightly soluble in water (1:2,500), soluble in alcohol (1:5), and soluble in almond and olive oils (1:30 to 1:50) (Ref. 2). Propylene glycol and polyethylene glycol may be used as water-miscible solvents for benzocaine.

(1) *Safety.* Clinical use and marketing experience have confirmed that benzocaine is safe for OTC use. It is one of the more widely used and safest topical anesthetics found in OTC preparations. It has been widely used since 1903. When applied, benzocaine is absorbed so slowly from oral tissues and wounds that reactions due to systemic toxic effects are virtually unknown (Refs. 1 and 5). The seizures and cardiac depressant characteristics of overdose of "caine" type drugs do not occur with benzocaine, and reports of such reactions with the use of benzocaine are nonexistent (Ref. 6).

Safety in part is due to hydrolysis of the drug by pseudocholinesterases in blood plasma which detoxifies esters of aminobenzoic acid.

Benzocaine has been administered orally to relieve stomach pain without any resulting toxic effects. The Panel is unaware of any fatalities due to oral ingestion of benzocaine and the lethal dose in man is not known.

Lethal doses have been determined in animals when benzocaine has been administered by various routes. When administered to rabbits, the LD_{50} for benzocaine was 146 mg/kg by the intratracheal route and 104 mg/kg intranasally (Ref. 7). In this study, a comparison with other commonly used anesthetics indicated that benzocaine is the safest.

Benzocaine therapy is not absolutely without adverse effects. Benzocaine in high doses may cause methemoglobinemia, because it can interfere with the reconversion of methemoglobin to hemoglobin (Refs. 1 and 5).

Cyanosis appears when 2 g or more of total adult hemoglobin have been converted to methemoglobin (the latter is incapable of carrying oxygen). Most reported systemic reactions were in infants under 6 months of age who were treated with benzocaine suppositories (Refs. 8 through 11). Infants under 4 months may be more susceptible than older infants, children, or adults because of their relative deficiency of DPNH-dependent methemoglobin reductase, an enzyme which protects against methemoglobin-inducing foreign compounds (Ref. 11). Some infants under 4 months of age may not have developed sufficient quantities of the reductase to prevent development of methemoglobinemia upon exposure to benzocaine.

A congenital deficiency of the enzyme in older children or in adults is rare. There are three cases reported in the literature of adults who developed methemoglobinemia within 3 hours of ingestion of benzocaine in 162.5-mg to 325-mg doses (Refs. 11 and 12). These reactions were of a mild nature.

When caused by the amounts absorbed from a single application of benzocaine, methemoglobinemia is not life threatening since the oxygen capacity is not significantly decreased. It is extremely unlikely that a dental application will cause methemoglobinemia if used according to proper directions.

The Panel recommends that infants under 4 months of age should not be treated with benzocaine except under the advice and supervision of a dentist or physician. No specific warning concerning methemoglobinemia is considered necessary.

Objection to the use of benzocaine as an oral mucosal analgesic is contained in reports of allergic responses and cross reaction with other anesthetics derived from para-aminobenzoic acid (Refs. 3 and 13 through 21). However, the total number of cases of allergy is small compared to the total number of applications of the drug. In the North American Dermatologic Study (Ref. 20), the incidence of benzocaine irritancy and sensitivity equals that of other commonly used drugs and is less than that of the more frequent sensitizers. The Panel recommends that a warning on allergy be included on the label.

Because benzocaine is a derivative of para-aminobenzoic acid, it may interfere with sulfonamides when taken concurrently because benzocaine would theoretically inhibit the antibacterial action of sulfonamides (Refs. 3 and 4). No warning is recommended by the Panel since there has been no demonstration that the interaction with sulfa actually occurs under conditions of dental use.

(2) *Effectiveness.* There are studies documenting the effectiveness of 5 to 20 percent benzocaine in appropriate vehicles (Refs. 22 through 26).

Benzocaine is an effective topical anesthetic which has an almost immediate onset of action and a short duration. Adriani (Ref. 23) has shown 20 percent benzocaine in polyethylene glycol ointment to have an onset of 15 seconds when applied to oral mucosa. The effect can be prolonged by keeping the preparation in contact with the mucosa (Ref. 23). The pain-relieving action of benzocaine is entirely within the mucous membranes, since the quantity circulating in the blood is insufficient to provide analgesia or anesthesia to other areas.

After application of 20 percent benzocaine ointment to the tongue, electrical stimulation produced no response (Ref. 24). Concentrations below 5 percent have not been shown to be effective after oral topical application, and concentrations above 20 percent gave no further enhancement of anesthetic activity (Ref. 25). Thus, benzocaine in the range of 5 percent to 20 percent is considered effective.

Duration of effectiveness is directly related to duration of contact with the mucosa, but effectiveness is also dependent on the formulation of the preparation (Refs. 1, 18, 26, and 27). The Panel concludes that when properly formulated, benzocaine is effective as an oral mucosal analgesic for the relief of oral discomfort.

(3) *Dosage.* Adults and children 4 months of age and older: Apply 5 to 20 percent benzocaine in appropriate vehicles to the affected oral mucosal area not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

The Panal also recommends the following warnings for benzocaine:

(a) "Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(b) "Fever and nasal congestion are not symptions of teething and may indicate the presence of infection. If these symptoms persist, consult your physician."

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b. *Butacaine sulfate.* The Panel concludes that a dosage of 0.75 g of a 4-percent ointment of butacaine sulfate is safe and effective for OTC use as an oral mucosal analgesic for the relief of oral discomfort as specified in the dosage section discussed below.

(1) *Safety.* Butacaine has a long history of use in dentistry (mainly under the supervision of a dentist) for denture sore spots and in extraction sites. Like other local anesthetics containing butyl groups, however, butacaine is highly toxic, having an LD_{50} and a convulsant dose less than that of cocaine but greater than that of tetracaine (Ref. 1). Butacaine can be absorbed very rapidly from mucous membranes (Ref. 2); therefore, topical application is equivalent to systemic administration. Even in professional use a total dose of 10 ml of a 2-percent preparation or its equivalent (200 mg) should never be exceeded when application is made to the oral mucosa (Ref. 2).

The Panel recommends that the OTC dose should not exceed application of 30 mg of butacaine sulfate (0.75 g of 4 percent ointment), and this amount must be supplied in single-use units (no more than 6 units per package) so that the user will not exceed the safe dose. This dose and packaging are considered to be safe for OTC use on a risk-to-benefit ratio, but dosage and packaging containing larger amounts are unsafe for OTC use.

Irritancy tests in the hamster cheek pouch proved positive (Ref. 3); however, further studies of the ointment in guinea pigs and in humans demonstrated no irritancy (Refs. 3 and 4).

Although evidence is provided that butacaine has low allergenic potential, it is possible for subjects to be allergic to butacaine in rare cases (Ref. 3). Also, if a patient is allergic to procaine, he or she may show cross-allergy with butacaine because of close chemical similarities. Therefore, the patient should be warned not to use the product if allergic to procaine, butacaine, benzocaine, or other "caine" anesthetics.

(2) *Effectiveness.* Butacaine is an effective topical anesthetic with a long history of use (Refs. 5 through 15). Tainter and Moose (Ref. 6) claimed that, based upon effectiveness ratings and upon the lack of irritancy of its vehicle, butacaine was the most useful topical anesthetic in their study.

Butacaine is listed as an accepted drug in the 37th edition of "Accepted Dental Therapeutics" (Ref. 10). There is also other published evidence of the usefulness of butacaine for anesthesia in various clinical conditions of the mucosal surfaces of the eye, nose, throat, and mouth (Refs. 11 through 15).

(3) *Dosage.* Adults and children 12 years of age and older: Apply 30 mg (0.75 g of a 4-percent ointment) not more often than every 3 hours and not more than three applications daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

In addition, the Panel recommends the following warnings for butacaine sulfate:

(a) "Do not use on children under 12 years of age unless recommended by a dentist or physician."

(b) "Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(c) "Do not use more than one unit at a time."

(d) "Do not repeat except after 3 hours."

(e) "Do not exceed 3 doses daily."

In addition, the labeling must not include the use of butacaine for teething pain.

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c. *Phenol preparations (phenol and phenolate sodium).* The Panel concludes

that 0.25 to 1.5 percent phenol in aqueous solution, up to 20 percent ethyl alcohol as a dental rinse, or up to 70 percent ethyl alcohol for direct application only, is safe and effective for OTC use as an oral mucosal analgesic for the relief of oral discomfort as specified in the dosage section discussed below.

(1) *Safety.* Clinical use and marketing experience have confirmed that aqueous phenol solutions are safe for application as an oral mucosal analgesic when used in concentrations ranging from a minimum of 0.25 percent to a maximum of 1.5 percent.

Maximum dosage should be restricted to that containing 600 mg within 24 hours for adults and children 12 years of age and older and 300 mg within 24 hours for infants and children 4 months to under 12 years of age.

The Panel reviewed reports that phenol and phenolic substances might have a carcinogenic or cocarcinogenic potential (Refs. 1 through 7). In addition to thorough study by the Panel, two experts were invited to consult with the Panel (Refs. 8 and 9).

Presentations by the consultants (Refs. 8 and 9) were especially helpful, since current views of earlier studies were presented. On the basis of data reviewed, the Panel concluded that if concentrations such as those recommended for mouth rinses or other OTC preparations are sufficiently low and the period of their use is restricted, there is no evidence that such use induces oral carcinoma (Refs. 3 and 8). The Panel determined that phenol should only be available at 1.5 percent or a lower concentration and that it should be limited to 7 days of continuous treatment, except under the supervision of a dentist or physician.

(2) *Effectiveness.* There are studies documenting the effectiveness of phenol as an oral mucosal analgesic (Refs. 10 through 14). Phenol has limited activity as a topical anesthetic. The local anesthetic activity of low concentrations is due to its ability to block nerve conductions (Refs. 10 and 11). However, if high concentrations are used, phenol demyelinates or otherwise destroys many types of nerve endings so that the ultimate action on nerve endings depends upon the concentration, contact time, and the vehicle used (Refs. 12 through 14).

(3) *Dosage*—(a) *Dental rinse.* 0.25 to 1.5 percent phenol in appropriate vehicles as directed. Dosage should not exceed 300 mg per day for children aged 6 to under 12 years. Dosage should not exceed 600 mg per day for adults and children aged 12 years and older.

(b) *Teething preparations.* 0.25 to 1.5 percent phenol in appropriate vehicles as directed. Dosage should not exceed 300 mg per day for infants and children 4 months to under 12 years of age.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. below—Category I Labeling.)

The Panel also recommends the following warnings for phenol preparations:

(a) "Fever and nasal congestion are not symptoms of teething and may indicate the presence of infection. If these symptoms persist, consult your physician."

(b) "Children between 6 and 12 years of age should be supervised in the use of this product as a dental rinse."

The labeling must also include adequate directions which will limit the dosage not to exceed 600 mg of phenol per day for adults and children 12 years of age and older and not to exceed 300 mg of phenol per day for infants and children 4 months to under 12 years of age.

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Category I Labeling

The Panel recommends the following Category I labeling for oral mucosal analgesic (topical anesthetic) active ingredients:

a. *Indications*—(1) *For all oral mucosal analgesics (topical anesthetics).* (a) "For the temporary relief of pain due to minor irritation or injury of soft tissue of the mouth."

(b) "For the temporary relief of pain due to minor dental procedures."

(c) "For the temporary relief of pain due to minor irritation of soft tissues caused by dentures or orthodontic appliances."

(d) "For the temporary relief of pain due to recurring canker sores when the condition has been previously diagnosed by a dentist."

(2) *For benzocaine and phenol used as oral mucosal analgesics (topical anesthetics) for teething pain.*

"For the temporary relief of sore gums due to teething in infants and children 4 months of age and older."

(3) *For oral mucosal analgesics (topical anesthetics) in denture adhesive products.*

"For the temporary relief of pain or discomfort of oral tissues due to dentures."

b. *Warnings*—(1) *For all oral mucosal analgesics (topical anesthetics).* (a) "Not to be used for a period exceeding 7 days."

(b) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(c) "Do not swallow."

(d) "Do not exceed recommended dosage."

(e) "Children under 12 years of age should be supervised in the use of this product."

(2) *For products containing "caine" derivatives.*

"Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacine, benzocaine, or other 'caine' anesthetics."

(3) *For products containing butcaine sulfate.*

(a) "Do not use in children under 12 years of age unless recommended by a dentist or physician."

(b) "Do not use more than one unit at a time."

(c) "Do not repeat except after 3 hours."

(d) "Do not exceed 3 doses daily."

(4) *For oral mucosal analgesics (topical anesthetics) for teething pain.*

"Fever and nasal congestion are not symptoms of teething and may indicate the presence of infection. If these symptoms persist, consult your physician."

(5) *For oral mucosal analgesics (topical anesthetics) in denture adhesive products.*

"See your dentist as soon as possible."

c. *Directions*—(1) *For products containing benzocaine.* Apply to the affected area not more than four times daily or as directed by a dentist or physician. For infants under 4 months of age there is no recommended dosage or treatment except under the advice and supervision of a dentist or physician.

(2) *For products containing butacaine sulfate.* Apply to the affected area. Do not use more than one unit at a time (each unit to contain no more than 30 mg butacaine sulfate). Do not apply more often than every 3 hours. Do not exceed three applications (90 mg) daily. Children under 12 years of age should not use this product except under the advice and supervision of a dentist or physician.

(3) *For products containing phenol.* (a) Apply to the affected area not more than six times daily. For adults and children 12 years of age and older, dosage should not exceed 600 mg of phenol per day. For infants and children 4 months to under 12 years of age, dosage should not exceed 300 mg of phenol per day. For infants under 4 months of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

(b) For phenol formulated as a dental rinse, dosage should not exceed 600 mg of phenol per day for adults and children 12 years of age and older. For children 6 to under 12 years of age, dosage should not exceed 300 mg of phenol per day. For children under 6 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

(4) *For oral mucosal analgesics (topical anesthetics) in denture adhesive products.* Apply on area of denture that comes in contact with sore gums.

d. *Package limit.* Products containing butacaine sulfate should be packaged in single-use units to contain no more than 30 mg each with no more than six units per package.

2. *Category II conditions under which oral mucosal analgesic active ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC drug products for the relief of oral dicsomfort effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

Camphor
Methyl salicylate

a. *Camphor.* The Panel concludes that camphor is not generally recognized as safe and effective for use as an OTC oral mucosal analgesic when applied topically to oral mucous membranes for the relief of oral discomfort. A camphor and phenol combination product was reviewed by the Panel. Although camphor was submitted as an active ingredient, the Panel considers phenol to be the active ingredient in this combination product, leaving camphor as a pharmaceutical aid which is intended to allow the use of a higher concentration of phenol.

(1) *Safety.* The Panel has reviewed copies of letters from Carol R. Angle, M.D., to the Hearing Clerk, FDA (Ref. 1) and to a former Director of FDA's Division of OTC Drug Evaluation (Ref. 2), a paper by W. J. Phelan (Ref. 3) which summarizes a report on poisoning by camphor products in 1974 by the National Clearinghouse for Poison Control Centers (Ref. 4), and a copy of the report on camphor from the minutes of the 16th meeting of the Advisory Review Panel on OTC Miscellaneous External Drug Products (Ref. 5). In general, that Panel's report concurred with this Panel's review of camphor regarding a pharmacological description of the ingredient and a discussion of its ingested toxicity. In particular, the report of the Miscellaneous External Panel cited numerous case studies of toxicity from camphor ingestions, most frequently of ingestions of camphorated oil, at least one of which goes back to 1848. The report of this Panel documents poisoning by solid camphor at even earlier dates.

In a number of instances, including those in the report submitted by Dr. Angle (Ref. 1), the ingested product contained one or more of other toxic substances in combination with camphor (Refs. 1, 2, and 3). In these instances it is difficult to ascribe the symptoms reported to only one agent. Gosselin et al. (Ref. 6) give camphor a toxicity rating of 4 (very toxic). However, many of the other combination ingredients, such as menthol, thymol, eucalyptol, methyl salicylate, and phenol, have also been given a toxicity raring of 4 by Gosselin et al. (Ref. 6). The 1974 report of the National Clearinghouse for Poison Control Center includes 244 ingestions of a combination product containing camphor and phenol and 89 ingestions of camphorated oil by children under 5 years of age (Ref. 4). As little as 0.7 to 1.0 g of camphor has proved fatal in children (Ref. 7). These data indicate that the problem of toxicity due to the ingestion of camphor is of current concern.

Phenol was accepted by the Panel for use at concentrations of 0.25 to 1.5 percent. A camphor-and-phenol-in-oil combination contains about 10 percent camphor and nearly 5 percent phenol. The research of Deichmann and associates (Refs. 8, 9, and 10) established that the presence of camphor-in-oil solutions of phenol brought into contact with an aqueous phase "holds" the phenol in the oil phase. In this way, the extent of the local action of phenol and the absorption of phenol through the tissues are considerably reduced from values found when phenol alone is present in this oil solution. The activity of camphor in this particular situation is that of a pharmaceutical necessity or pharmaceutical aid. Camphor is used for the same purpose (pharmaceutical aid) in camphorated parachlorophenol.

(2) *Effectiveness.* It is stated that camphor applied locally has a mild anesthetic action and that its application to the skin may be followed by numbness (Ref. 11). Phenol, when mixed with camphor, loses a great deal of its caustic effect but retains most of its analgesic and antiseptic action (Ref. 7).

The Panel considered whether or not there is any rationale for using a mixture of 4.66 percent phenol with 10.8 percent camphor (in liquid petroleum) to be applied in the mouth. Deichmann and Miller (Ref. 12) reorted that when a similar solution was equilibrated with an aqueous phase only 22 percent of the phenol entered the aqueous phase (equal to approximately 1 percent phenol in the aqueous phase). The availability of phenol may be more or less then 22 percent when the combination product is in contact with mucous membranes of the mouth. However, if one assumes that approximately 22 percent of the phenol in the combination enters the aqueous

phase and is available, then an aqueous solution of 1 percent phenol should probably be as useful as the phenol-camphor-liquid petrolatum combination used to relieve discomfort of minor irritation of oral soft tissues.

(3) *Evaluation.* The Panel concludes that the risk of accidental ingestion of camphor as well as phenol in the combination is not balanced by any increased benefit of the combination over use of small quantities of 1 percent phenol alone. The Panel therefore recommends that camphor be placed in Category II on the basis of the risk-to-benefit ratio. As an inactive ingredient the amount of camphor allowed to impart flavor or odor should be limited to less than 0.2 percent.

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b. *Methyl salicylate.* The Panel concludes that methyl salicylate is not generally recognized as safe and effective for OTC application as an oral mucosal analgesic.

(1) *Safety.* Methyl salicylate causes irritation with the possibility of local tissue damage when applied to mucous membranes (Refs. 1 and 2). Because of the reputed systemic toxicity of methyl salicylate, the Panel recommends that any dentifrice or dental care agent containing this substance as a pharmaceutical aid (i.e., flavoring agent) be in conformity with all pertinent regulations for its use as such.

(2) *Effectiveness.* There are no studies that indicate that topically applied methyl salicylate provides an anesthetic effect. It apparently acts only as a counterirritant (Refs. 2 and 3).

(3) *Evaluation.* Methyl salicylate is an irritant when applied topically, possibly causing local tissue damage. The Panel concludes that there is no rational use of methyl salicylate as an OTC oral mucosal analgesic.

References

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of a product are unsupported by scientific data and, in some instances, by sound theoretical reasoning. The Panel concludes that such labeling should be removed from the market.

The Panel considers the following examples of claims to be misleading and unsupported by scientific data:

"For quick temporary relief of pain and soreness due to minor irritation of teeth and gums."

"Especially soothing after extractions or for minor gum boils."

"For temporary relief of cavity toothache."

"For rapid and effective relief of sore gums."

"For sore gums following tooth extractions."

"For use after teeth extraction."

"Hold in mouth as long and as frequently as necessary, then rinse." This is inconsistent with the directions of use proposed by the Panel.

"Eases pain due to cavities fast."

"Fast relief from toothache due to cavities."

"Temporary relief for toothache due to cavities."

"Gives quick relief that lasts for hours."

"For fast, temporary relief of minor mouth or gum soreness." The claim is too vague; it must be more specific.

"Subdues the throbbing ache of sore, swollen gums." The claim is too vague; gums may be infected or a deeper problem may exist.

"Stops baby's tears within seconds."

"Relief of discomfort of minor gum disorders before and after gingivectomy." Gingivectomy should be treated by a dentist.

The following claim encourages the consumer to avoid dental care by promoting use beyond the 7-day limit established by the Panel for safe use: "Holds dentures comfortably in place." This claim is acceptable when a denture adhesive is combined with an oral mucosal analgesic only for short-term use.

The Panel considers claims which imply a superiority in onset of action, such as "quicker," "more quickly," and "faster," to be misleading because all oral mucosal analgesics have a rapid onset.

The Panel considers the following terms to be vague and not definitive of the condition for which relief is sought: "sore spots," "anti-irritation," "comfortable adjustment," "helps comfortable adjustment," "stops pain," "soothes sore gums," "special," "unaccustomed use," "alleviates pain."

The following claims are for conditions that require the advice of a dentist: "gum boils," "gum or gingival inflammation," and "abscesses."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I except as noted for specific pharmacotherapeutic groups.

The Panel concludes that adequate and reliable scientific evidence is not available at this time to permit final classification of the ingredients and conditions listed below. Marketing need not cease during this time if adequate testing is undertaken. If adequate effectiveness data are not obtained within 2 years, however, the ingredients and conditions listed in this category should no longer be marketed in OTC products.

Category III Active Ingredients

Benzyl alcohol
Cresol

Thymol preparations (thymol and thymol iodide)

a. *Benzyl alcohol.* The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of benzyl alcohol at a concentration of 1 to 3 percent for OTC use as an oral mucosal analgesic for the relief of oral discomfort.

(1) *Safety.* There are insufficient data to establish the safety of 1 to 3 percent benzyl alcohol for OTC use as an oral mucosal analgesic.

Since animal studies suggest that ingestion of benzyl alcohol 1 mL/kg may be fatal (Ref. 1), and since package sizes that will provide more than 30 mL of a 2-percent solution or 60 mL of a 1-percent solution are unnecessary and may be a potential risk for accidental ingestion by young children, the Panel recommends that package size be limited to that containing a total of 0.6 mL of benzyl alcohol.

Benzyl alcohol in a 100-percent concentration is irritating to tissue; injected subcutaneously or intramuscularly the drug produces local necrosis (Refs. 1, 2, and 3). Benzyl alcohol given to dogs by stomach tube in doses of 0.2 to 0.5 mL/kg of body weight produced vomiting and defecation. These effects were attributed to local irritation of gastrointestinal mucosa because subcutaneous and intramuscular administration of these same doses did not produce these gastrointestinal reactions (Ref. 3). Benzyl alcohol applied to the tongue or lip of humans produces a primary irritating effect (Ref. 1). Instillation of the drug into the conjunctival sac of a rabbit was followed by some necrosis of the cornea (Ref. 1).

Benzyl alcohol in a concentration of 1 to 4 percent is included in injections, for subcutaneous or intramuscular administration, for its local anesthetic and bacteriostatic actions (Refs. 4, 5, and 6). Benzyl alcohol is categorized as a pharmaceutic aid (bacteriostatic) for injections in "National Formulary XIV," but the concentration to be used is not specified. Benzyl alcohol was categorized as a local anesthetic in the 10th, 11th, and 12th editions of the "National Formulary X." Category designation was begun with the 10th edition of the "National Formulary." In an early study, aqueous solutions of 1 to 3 percent benzyl alcohol were injected, apparently by infiltration, to provide local anesthesia for surgery in 33 patients (Ref. 1). This study reported that these solutions did not "produce any marked irritation or destruction of the tissues into which they were injected."

Upon application to the human cornea, 1 percent benzyl alcohol in isotonic saline produced transient pain described as "fairly severe smarting" (Ref. 7). Studies in which 1-percent or 1- to 4-percent solutions of benzyl alcohol were applied to corneas of experimental animals showed results varying from no irritation to reddening of the conjunctiva (Refs. 1 and 8). The more severe reactions were perhaps due to some deterioration of the benzyl alcohol under the conditions of storage. Since the drug is slowly soluble in water only to the extent of 1 g in 25 to 30 mL, aqueous preparations containing more than 3 to 4 percent benzyl alcohol are likely to contain some undissolved benzyl alcohol which may produce irritation (Refs. 4, 5, and 6).

There have been a few studies that evaluated the tissue irritation potential of benzyl alcohol in nonaqueous solvents. Application of 50 percent benzyl alcohol in 95 percent ethanol to the mucosa of the mouth or gums of 61 patients produced irritation in 31 percent of the patients and hyperemia in 11 percent of the patients (Ref. 9). That 50 percent benzyl alcohol was irritating is far from conclusive, however, because concurrently with the benzyl alcohol solution tests, 95 percent ethanol was applied on the opposite side of each patient's mouth. The ethanol "control" produced irritation in 40 percent of the patients and hyperemia in 18 percent of the patients. In a subsequent report of 156 patients who were tested with 95 percent ethanol, 38 percent responded with irritation and 14 percent with hyperemia; of 506 "aqueous controls," 14 percent showed irritation and 7 percent showed hyperemia (Ref. 10). In addition to the 506 patients treated with "aqueous control" (water or 0.9-percent sodium chloride solutions with color or a flavor or "fluorescent"), 70 patients were treated with "Liquor Alkalines Aromaticus," "National Formulary V." or "National Formulary VI." Since this solution may possibly be irritating, these patients were not included in the figures stated in this document.

A preparation containing 1 percent benzyl alcohol, together with benzocaine and clove oil, in an adhesive base intended for application to the oral mucous membrane, was subjected to sensitization and irritation tests (Ref. 11). At the 24-hour and subsequent observation periods after application of the material to the skin, eyes, and oral mucous membranes of experimental animals, no irritation was observed. However, no data were presented on any observations prior to the 24-hour period. Guinea pig sensitization tests were negative.

The studies cited above show that undissolved benzyl alcohol is a potent irritant. Aqueous solutions in concentrations from 1 to 3 percent of benzyl alcohol may produce variable degrees of irritation to soft tissues.

(2) *Effectiveness.* Benzyl alcohol does possess local anesthetic activity, but the concentrations (in aqueous and nonaqueous solvents) needed to provide relief of pain of oral soft tissues have not been established. Standard reference sources attribute local anesthetic activity to benzyl alcohol and cite uses by injection, by application to mucous membrances, and by application to the skin as an antipruritic (Refs. 4, 5, and 6). For OTC dental and related use, benzyl alcohol is included in preparations for toothache, for sore mouth due to dentures, and for cold sores.

Two to 4 percent benzyl alcohol in saline produced anesthesia in dogs when injected subdurally (Ref. 13). Concentrations of 1 to 3 percent benzyl alcohol were injected to provide anesthesia for surgical procedures apparently be infiltration in 33 humans (Ref. 1).

Topical applications of solutions of benzyl alcohol are reported to be uncertain in effect (Ref. 4). In descriptive, uncontrolled studies in experimental animals and humans, benzyl alcohol applied topically in 1- to 2-percent solutions was reported to produce complete or partial anesthesia of skin (Refs. 1 and 7), motor nerves, and sensory nerves of frogs (Ref. 1); corneas of animals (Refs. 1, 7, and 8); and oral mucous membranes of humans (Refs. 1 and 7). In another uncontrolled study, a 10-percent solution of benzyl alcohol applied to the tip of the tongue of human subjects provided a short period of anesthesia (Ref. 14). Application of pure benzyl alcohol to the nostrils, skin, tongue, or lips of humans was followed by some degree of anesthesia (Refs. 1 and 7).

In the only controlled, double-blind studies of local anesthetic activity of topical benzyl alcohol which could be found in the literature, a 50-percent solution of benzyl alcohol in 95 percent ethanol was compared with placebo aqueous solutions and with 95 percent ethanol without benzyl alcohol (Refs. 9 and 10). The solutions were applied to the oral mucous membranes of humans. Complete or partial anesthesia was reported by 43 percent of the 576 patients receiving various placebo aqueous solutions, 78 percent of the 156 patients receiving 95 percent ethanol

solutions and 79 percent of the 61 patients treated with 50-percent benzyl alcohol in 95 percent ethanol (Ref. 10). In the initial study in this series, patients were concurrently treated on opposite sides of the mouth with 50 percent benzyl alcohol in 95 percent ethanol and with 95 percent ethanol (Ref. 9). Of the 61 patients tested, 67 percent experienced complete or partial anesthesia with 95 percent ethanol and 79 percent reported some anesthesia with 50 percent benzyl alcohol in 95 percent ethanol. No statistics were presented, and the benzyl alcohol concentration was very high.

Since benzyl alcohol solutions stored in soft glass containers have been shown to increase in pH and decrease in anesthetic activity, the Panel believes there may be stability problems with benzyl alcohol solutions in some dosage forms or in some types of packaging. Therefore, the stability of benzyl alcohol in the particular dosage form and packaging intended for marketing should be established (Ref. 8).

(3) *Proposed dosage.* Adults and children 2 years of age and older: Apply 1 to 3 percent benzyl alcohol to the affected area not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

In addition, products containing benzyl alcohol should contain no more than a total of 0.6 mL (30 mL of a 2-percent solution or 60 mL of a 1-percent solution) of benzyl alcohol in a container capable of maintaining stability of the product.

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to establish the safety and effectivenesss of 1 to 3 percent benzyl alcohol as an oral mucosal analgesic. Data to demonstrate safety and effectiveness as an oral mucosal analgesic will be required in accordance with the guidelines set forth below. (See part IV. paragraph C. below—Data Required for Evaluation.)

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b. *Cresol.* The Panel concludes that there are insufficient data available to permit the final classification of the safety and effectiveness of cresol at a concentration of 0.25 to 1.0 percent for OTC use as an oral mucosal analgesic for the relief of oral discomfort.

(1) *Safety.* Cresol, a mixture of 2-, 3-, 4-methylphenols, is obtained by fractional distillation of coal tar or petroleum (Refs. 1 and 2). Cresol is a protoplasmic poison resmbling phenol in its effects, although it may be slightly more corrosive than phenol and its systemic effects may be slightly milder because of slower absorption (Refs. 3 and 4). In an invitro test, 0.25 percent cresol, 0.54 percent phenol, 0.3 percent *m*-cresol, and 1.2 percent benzyl alcohol produced total hemolysis of erythrocytes (Ref. 5). In a study of carcinogenic activity of phenol and related compounds on mouse skin, each of the three cresols was reported to have the same order of "promoting" activity as phenol (Ref. 6).

On the skin, cresol produces erythema, burning, and numbness (Ref. 2). If ingested, cresol causes a severe burning sensation in the mouth and upper abdomen, dysphagia (difficulty in swallowing), vomiting, and diarrhea (Ref. 2). Chronic poisoning (either by ingestion or percutaneous absorption) may produce widely varied reactions such as gastrointestinal disturbances, central nervous system dysfunctions, skin eruptions, jaundice, oliguria, and uremia (Ref. 7). At least one death has been reported from topical application of cresol to a large area of the body surface of a child (Ref. 8). Irritation of periapical tissues may occur if cresol is used in root canal therapy (Ref. 1).

Dilute solutions of cresol are used in therapeutics, although the Panel found no data relating to safety of such solutions. Cresol is sometimes used in concentrations of 0.25 to 0.5 percent as a bacteriostatic agent in parenteral solutions. A saponated solution containing 0.5 percent cresol has been used for application to wounds, and a saponated solution containing 0.1 percent cresol has been used as a vaginal douche (Ref. 2).

The maximum dosage for cresol should be restricted to no more than 400 mg within 24 hours for adults and children over 12 years of age and 200 mg within 24 hours for children 6 to 12 years of age.

(2) *Effectiveness.* Early studies in experimental animals and man suggest that cresol solutions have some local anesthetic activity (Refs. 9 through 12). Gurney (Ref. 13) reports that cresols have been used as mild pulpal analgesics and that they exhibit a demonstrable analgesia when applied under proper conditions. He notes that the analgesia may be easily seen with application of cresol to irritated pulps of primary teeth, but it is very difficult to demonstrate analgesia with permanent teeth. Gurney's paper (Ref. 13) did not include clinical studies.

The Panel conducted a thorough search of the scientific literature for clinical studies of cresol as a local anesthetic for use on soft oral tissue. Such studies were not found. One submission included one unpublished clinical study of the obtundent qualities of a product containing cresol and boric acid (Ref. 14). This clinical study apparently included more than 120 patients, but it was uncontrolled, not well documented, and evaluations were subjective.

(3) *Proposed dosage.* Adults and children 6 years of age and older: Apply 0.25 to 1.0 percent cresol in aqueous solution to the affected area. The total amount to be applied in a 24-hour period should not exceed 400 mg for adults and

children over 12 years of age or 200 mg for children 6 to 12 years of age.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling).

In addition, the panel recommends the following warning for cresol:

"Do not use in children under 6 years of age unless recommended by a dentist or physician."

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to establish the safety and effectiveness of cresol as an oral mucosal analgesic. Data to demonstrate safety and effectiveness of cresol as an oral mucosal analgesic will be required in accordance with the guildelines set forth below. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 209, 1977.

(2) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 355, 1973.

(3) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 37th Ed., American Dental Association, Chicago, p. 63, 1977.

(4) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, Section II, p. 129, 1976.

(5) Ansel, H. C., and D. E. Cadwallader, "Hemolysis of Erythrocytes by Antibacterial Preservatives," *Journal of Pharmaceutical Sciences,* 53:169–172, 1964.

(6) Boutwell, R. K., and D. K. Bosch, "The Tumor-promoting Action of Phenol and Related Compounds for Mouse Skin," *Cancer Research,* 19:413–424, 1959.

(7) Windholz, M., et al., "The Merck Index," 9th Ed., Merck and Co., Rahway, NJ, p. 335, 1976.

(8) Arthur, A. B., "A Hazard of Cresol," *New Zealand Medical Journal,* 76:450, 1972.

(9) Ikebe, S., "Experimental Study on Surface Anesthesia of the Outer Ear Passage in Guinea Pigs," (abstract), *Chemical Abstracts,* 29:2599, 1935.

(10) Ikebe, S., "Experimental Study on Surface Anesthesia in the External Ear in the Guinea Pig: IV.," (abstract), *Chemical Abstracts,* 29:7489, 1935.

(11) Kasuga, E., "Percutaneous Anesthesia," (abstract), *Chemical Abstracts,* 34:7428, 1940.

(12) Sato, S., "Physicochemical Studies on the Anesthetic Potency of Phenolic Compounds: II. Anesthetic Potency on Sciatic Nerve of Frog," (abstract), *Chemical Abstracts,* 64:20415, 1966.

(13) Gurney, B. F., "Substituted Phenols: Part Two—Cresols, Cresylacetate, Formocresol," *Dental Digest,* 78:314–316, 1972.

(14) OTC Volume 080013.

c. *Thymol preparations (thymol and thymol iodide).* The Panel concludes that thymol preparations in concentrations up to 20 percent are safe but that there are insufficient data available to permit final classification of their effectiveness of OTC use as oral mucosal analgesics.

(1) *Safety.* The acute toxicity of thymol in a solution of propylene glycol was determined by oral administration to experimental animals (Ref. 1). Groups of 10 young adult Osborne-Mendel rats, evenly divided by sex, were fasted for approximately 18 hours and given the test material. The LD_{50} was 0.98 g/kg with a death time ranging from 4 hours to 5 days. The toxic signs with high dose consisted of depression, ataxia (irregularity of muscle action), and coma.

The minimum lethal dose of thymol when administered by the oral route has been reported to be 800 mg/kg in the mouse, 750 to 1,000 mg/kg in the rabbit, and 250 mg/kg in the cat (Ref. 2).

Thymol is considered to be less toxic than phenol. In humans fats and alcohol increase absorption and aggravate the toxic symptoms (Ref. 3). Thymol is completely absorbed from the intestine. It is excreted in the urine as the sulfate and glucuronide together with some thymol-quinone. About half of a dose is destroyed in the body. Thymol is an irritant to the kidney (Ref. 3).

There are no apparent studies on thymol iodide; however, when thymol iodide was fed to rats for 5 weeks in a study designed to demonstrate iodide availability, there was considerable uptake of iodide by the thyroid (Ref. 4).

Boutwell and Bosch (Ref. 5) studied over 50 compounds related to phenol for their ability to promote the development of skin tumors following a single initiating dose of dimethylbenzanthracene. One of these compounds tested (2-isopropyl-4-methyphenol) is closely related to thymol. When dissolved in 16 percent benzene and applied weekly for 12 weeks to mice, 19 percent developed skin tumors and 6 percent (1 of 16 mice) developed a carcinoma.

"The United States Dispensatory" (Ref. 6) states that thymol can cause nausea, vomiting, albuminuria, headache, tinnitus, dizziness, muscular weakness, a thready pulse, slow respiration, and a fall in body temperature. It further states that the heart is depressed by "therapeutic" doses. Thymol, used systemically in the treatment of mycosis, has been given as divided oral doses consisting of 1 to 2 g daily being administered in courses of 2 of each 3 days. It has also been used as an intestinal antiseptic, in doses up to 120 mg.

Gleason et al. (Ref. 7) state that the toxicity of thymol is believed to lie on the borderline between toxicity classes 3 and 4 (moderately toxic and very toxic).

Thymol is less toxic than phenol and larger doses may be taken (Ref. 3). It is generally an irritant to tissues, and given orally it is an irritant to the gastric mucosa. Rashes from thymol are not uncommon (Ref. 3). It was formerly used for the treatment of hookworm infestations, but had to be used in such large doses that there was danger of serious, even fatal, poisoning. Oral doses stimulate peristalsis and may cause diarrheal stools (Ref. 6).

Thymol should not be given by mouth to persons with gastrointestinal disorders or impared kidney function. It should be given with care to patients with heart disease (Ref. 3). However, the amounts used topically in the oral cavity are insufficient to cause problems for these individuals.

(2) *Effectiveness.* Thymol is used chiefly as a deodorant in antiseptic mouthwashes and gargles. Mixed with phenol and camphor, thymol is used in dentistry to prepare cavities before filling, and it is mixed with zinc oxide to form a protective cap for the dentine (Ref. 3).

There are reports of use of thymol or thymol iodide in oral mucosal analgesic products, but there are insufficient data to establish effectiveness (Refs. 1 through 7). Since eugenol and thymol are chemically similar, the possibility of effectiveness as an oral mucosal analgesic is suggested and has, in fact, been frequently associated with professional use for this purpose (Ref. 3).

(3) *Proposed dosage.* Adults and children 2 years of age and older: Apply a maximum of 20 percent thymol or thymol iodide to the affected area not more than four times daily.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal analgesic active ingredients. (See part IV. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that there are insufficient data to establish the effectiveness of thymol preparations as oral mucosal analgesics. Data to demonstrate effectiveness as an oral mucosal analgesic will be required in accordance with the guidelines set forth below. (See part IV. paragraph C. below—Data Required for Evaluation.)

References

(1) Jenner, P. M., et al., "Food Flavourings and Compounds of Related Structure: I. Acute Oral Toxicity," *Food and Cosmetics Toxicology,* 2:327–343, 1964.

(2) Spector, W. S., "Handbook of Toxicology: Volume I," W. B. Saunders Co., Philadelphia, pp. 298–301, 1956.

(3) Blacow, N. W., and A. Wade, "Martindale: The Extra Pharmacopeia," 26th Ed., The Pharmaceutical Press, London, p. 212, 1972.

(4) Mittler, S., and G. H. Benham, "Nutritional Availability of Iodine from Several Insoluble Iodine Compounds," *Journal of Nutrition*, 53:53–58, 1954.

(5) Boutwell, R. K., and D. K. Bosch, "The Tumor-promoting Action of Phenol and Related Compounds for Mouse Skin," *Cancer Research*, 19:413–424, 1959.

(6) Osol, A., R. Pratt, and A. R. Gennaro, "The United States Dispensatory," 27th Ed., J. B. Lippincott Co., Philadelphia, p. 1190, 1973.

(7) Gleason, M. N., et al., "Clinical Toxicology of Commercial Products," 3d Ed., Williams and Wilkins, Baltimore, p. 143, 1969.

Category III Labeling

None.

C. Data Required for Evaluation

The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

Adriani et al. (Ref. 1) have studied surface anesthetic activity in great depth, and their research provides a methodology which the Panel recommends for testing oral mucosal analgesics. The selection of patients, study method, and interpretation of data are also included in these investigations and should serve as a model.

In addition, data to demonstrate safety of cresol and benzyl alcohol should include well-designed studies demonstrating lack of irritation of oral mucous membranes in humans under conditions of proposed use.

The Panel concludes that 3 years after publication of the proposed rules is an adequate time period for the completion of studies and the submission of data.

Reference

(1) Adriani, J., et al., "The Comparative Potency and Effectiveness of Topical Anesthetics in Man," *Clinical Pharmacology and Therapeutics*, 5:49–62, 1964.

V. Oral Mucosal Protectants

A. General Discussion

Oral mucosal protectants are insoluble, pharmacologically inert substances that form adherent, continuous, flexible, or semirigid coats when applied to the oral mucous membranes (Ref. 1). These coatings help to protect the irritated areas of the mouth from further irritation from chewing, swallowing, and other mouth activity. When applied locally to the oral mucous membranes, they can provide temporary relief of discomfort of minor thermal or chemical burns, irritations, or ulcerations resulting from mechanical trauma and aphthous ulcerations (canker sores).

Oral mucosal protectants may be applied by health professionals such as dentists or physicians in treating their patients, or they may be applied as self-medication by the patients themselves. The Panel has considered the various conditions where such protectants might be used professionaly and on a self-medication basis. The Panel concludes that oral mucosal protectants available as OTC products may be locally applied to oral mucous membranes for the temporary relief of discomfort from minor burns of the oral mucosa and minor injuries or irritations of the mouth. The Panel also concludes that the treatment of persistent aphthous ulcerations and other mouth ulcerations depends upon a professional diagnosis and that such treatment should be under the advice of a dentist or physician. Therefore, OTC labeling should include the use of a protectant for these indications only if the condition has been previously diagnosed by a dentist or physician. (See part V. paragraph B.1. below—Category I Labeling.)

It is possible that solutions of protective substances might serve as carriers of other medicinal materials. For example, an oral mucosal analgesic such as benzocaine might be included in the formulation to add its effect to the protectant in relieving pain from irritation.

Benzoin tincture and compound benzoin tincture are generally recognized as effective as oral mucosal protectants by the Panel on the basis of published observations by dental experts. (See part V. paragraph B.1. below—Benzoin preparations (benzoin tincture and compound benzoin tincture).)

The effectiveness of Category III protectants must be established by demonstrating that the agent provides a suitable coating when applied to the oral mucosa protecting minor irritations and injuries from further irritation. Effectiveness should be established by 2 well-controlled clinical studies, and 2 years should be allowed for such studies. (See part V. paragraph C. below—Data Required for Evaluation.)

Reference

(1) Harvey, S. C., "Topical Drugs," *in* "Remington's Pharmaceutical Sciences," 15th Ed., Edited by A. Osol et al., Mack Publishing Co., Easton, PA, pp. 712–714, 1975.

B. Categorization of Data

1. *Category I conditions under which oral mucosal protectant active ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federal Register.**

Category I Active Ingredient

Benzoin preparations (benzoin tincture and compound benzoin tincture)

Benzoin preparations (benzoin tincture and compound benzoin tincture). The Panel concludes that benzoin preparations are safe and effective for OTC use as oral mucosal protectants for the relief of oral discomfort as specified in the dosage section discussed below.

For the purpose of this review, compound benzoin tincture is considered as a single entity since the proportion of ingredients has been fixed over many decades. Also, the Panal does not differentiate the safety and effectiveness data of benzoin tincture and compound benzoin tincture. Compound benzoin tincture, which is official in the "United States Pharmacopeia" (Ref. 1), contains 10 percent benzoin, 2 percent aloe, 8 percent storax, 4 percent tolu balsam, and 74 to 80 percent ethanol (Ref. 1). Benzoin tincture contains 20 percent benzoin and 75 to 83 percent alcohol. Benzoin tincture is no longer official, but it is still available on the market in the United States.

(1) *Safety.* Clinical use and marketing experience have confirmed that benzoin preparations are safe for OTC use. There is little information in the literature on the safety and toxicity of benzoin and the other constituents that make up the compound tincture.

Gosselin et al. (Ref 2) assigns benzoin, storax, and tolu toxicity ratings of 3 (moderately toxic); aloe or aloin has a toxicity rating of 4 (very toxic) when ingested orally. Drugs with a toxicity rating of 3 are considered to have probable lethal dosage of 500 mg to 5 g/kg body weight. Drugs with a toxicity rating of 4 are considered to be probably lethal in doses of 50 to 500 mg/kg body weight.

Although the toxicity ratings are given on the basis of the ingredients of the tincture and the compound tincture, Gosselin et al. (Ref. 2) state that alcohol is expected to be responsible for the major toxic effects of ingestion of these tinctures.

No reports giving evidence of chronic toxicity of benzoin, storax, aloe, and tolu were found in the literature.

Hypersensitively and irritation from topical use of the benzoin tinctures were reported in two papers. In a study involving 413 patients with contact dermatoses, it was found that two showed allergic reactions to patch tests of compound benzoin tincture (Refs. 3 and 4). Another report states that a 22-year-old man exhibited sensitivity to benzoin and to other gums and resins when given a patch test (Refs. 3 and 5). He had previously developed acute eczematous contact dermatitis 23 days following the application of benzoin tincture to the skin under a plaster cast. A patch test also demonstrated cross-sensitivity to myrrh.

Dental clinicians have, however, been using and recommending benzoin tinctures for topical application to oral tissues for many years, and the use has apparently been without adverse effects. Furthermore, very small quantities of the tinctures are used per application when applied locally to oral mucous membranes. In spite of the high alcohol content, benzoin tincture and compound benzoin tincture are considered safe for occasional application to small areas of the oral mucosa.

Tinctures of benzoin should be packaged in well-closed containers of 30 mL or less and have child-proof caps.

(2) *Effectiveness.* There are studies documenting the effectiveness of compound benzoin tincture (Refs. 3 and 6 through 21). In the treatment of intraoral lesions, the tissues are first dried because benzoin is not water soluble, and then the tincture is applied. In this manner a protective, although transient, coating is deposited on the area of application. Although there are no double-blind, well-controlled clinical studies to support the effectiveness of the benzoin tinctures as protectants, the use of benzoin tincture and compound benzoin tincture for the treatment of lesions of oral mucous membranes has been successful for a long time in dentistry. Standard references list a number of dental uses for benzoin tinctures in providing relief from oral discomfort. The tincture or the compound tincture used full strength, though often mixed with glycerin and water, is applied locally as a protective in small cuts, cutaneous ulcers, and fissures of the lips (Refs. 2 and 6 through 9). Applied full strength, the tinctures are said to have protective, stimulating, and styptic activity (Refs. 3, 8, and 10).

Benzoin tincture has been used for pulp capping and for saturating intraoral dressings used in treatment of painful extraction wounds (Refs. 8 and 11). Application of compound benzoin tincture has been widely recommended as a protective for relief of discomfort of chemical or thermal burns (Refs. 12 through 15), of minor mechical or physical trauma (Refs. 14, 15, and 16), and of irritations of the oral mucosa (Refs. 9 and 17).

Compound benzoin tincture has also been recommended as a protective for relief of discomfort from aphthous ulcers (Refs. 3, 6, 7, 18, and 20) and of oral herpes simplex ulcers (Refs. 7, 10, and 21). The Panel has concluded, however, that recurring aphthous stomatitis (canker sores) is an OTC indication for protectives only if the condition has been previously diagnosed by a dentist or physician. Indications for oral herpes simplex ulcers were deferred to the Advisory Review Panel on OTC Miscellaneous External Drug Products.

Benxoin tincture and compound benzoin tincture should only be used as a single ingredient at full strength, because combining benzoin with another ingredient will dilute the product and reduce its effectiveness as a protectant. Literature cited has described only the use of full-strength tinctures as protectives in applications to the oral mucosa. Effectiveness of tinctures with concentrations less than full/strength remains to be shown.

(3) *Dosage.* Adults and children 6 months of age and older: Apply to the affected area undiluted not more often than every 2 hours.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing oral mucosal protectant active ingredients. (See part V. paragraph B.1. below—Category I Labeling.)

References

(1) "The United States Pharmacopeia," 19th Ed., United States Pharmacopeial Convention, Rockville, MD, p. 51, 1975.

(2) Gosselin, R. E., et al., "Clinical Toxicology of Commercial Products," 4th Ed., Williams and Wilkins, Baltimore, section II, pp. 156–157 and 166, section III, pp. 140–143, 1976.

(3) Blacow, N. W., and A. Wade, "Martindale: The Extra Pharmacopoeia," 26th Ed., The Pharmaceutical Press, London, pp. 311–312 and 314–315, 1972.

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(8) Dobbs, E. C., "Pharmacology and Oral Therapeutics," 11th Ed., C. V. Mosby Co., St. Louis, pp. 288 and 523, 1956.

(9) Bernstein, H. B., "Agents Acting Locally on Skin or Mucous Membranes," *in* "Pharmacotherapeutics of Oral Disease," Edited by A. H. Kutscher, E. V. Zegarelli, and G. A. Hyman, McGraw-Hill Book Co., New York, pp. 116–124, 1964.

(10) Syrop, H. M., "Secondary Herpes," *in* "Pharmacotherapeutics of Oral Disease," Edited by A. H. Kutscher, E. V. Zegarelli, and G. A. Hyman, McGraw-Hill Book Co., New York, pp. 354–355, 1964.

(11) Rothenberg, F., "Sutures, Packings, and Dressings," *in* "Pharmacotherapeutics of Oral Disease," Edited by A. H. Kutscher, E. V. Zegarelli, and G. A. Hyman, McGraw-Hill Book Co., New York, pp. 597–599, 1964.

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(13) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 36th Ed., American Dental Association, Chicago, pp. 265–266, 1975.

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(15) Manhold, J. H., Jr., and T. E. Bolden, "Physical Destruction of Tissue," *in* "Pharmacotherapeutics of Oral Disease," Edited by A. H. Kutcher, E. V. Zegarelli, and G. A. Hyman, McGraw-Hill Book Co., New York, pp. 373–374, 1964.

(16) Kutscher, A. H., E. V. Zegarelli, and G. A. Hyman, "Epitome, Vehicle Protectants," *in* Pharmacotherapeutics of Oral Disease," Edited by A. H. Kutscher, E. V. Zegarelli, and G. A. Hyman, McGraw-Hill Book Co., New York, pp. 31–32, 1964.

(17) Dobbs, E. C., "Pharmacology and Oral Therapeutics," 12th Ed., C. V. Mosby Co., St. Louis, p. 133, 1961.

(18) Zegarelli, E. V., A. H. Kutscher, and H. F. Silvers, "Recurrent Ulcerative Stomatitis," *in* "Pharmacotherapeutics of Oral Disease," Edited by A. H. Kutscher, E. V. Zegarelli, and G. A. Hyman, McGraw-Hill Book Co., New York, pp. 377–378, 1964.

(19) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 36th Ed., American Dental Association, Chicago, p. 270, 1975.

(20) Wood, R. H., "Aphthous Ulceration of the Mouth," *British Medical Journal,* 2:1304, 1957.

(21) Council on Dental Therapeutics, "Accepted Dental Therapeutics," 36th Ed., American Dental Association, Chicago, pp. 259–260, 1975.

Category I Labeling

The Panel recommends the following Category I labeling for oral mucosal protectant active ingredients:

a. *Indications.* (1) "Forms a coating over a wound."

(2) "Protects against further irritation."

(3) "For temporary use to protect wounds caused by minor irritations or injury."

(4) "For protecting recurring canker sores when the condition has been previously diagnosed by a dentist."

b. *Warnings.* (1) "Not to be used for a period exceeding 7 days."

(2) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(3) "Do not swallow."

(4) "Do not exceed recommended dosage."

(5) "Children under 12 years of age should be supervised in the use of this product."

c. *Directions.* For adults and children 6 months of age and older: Dry the affected area, saturate a cotton applicator with medication, and apply to the affected area not more often than every 2 hours. For children under 6 months of age, there is no recommended dosage except under the advice and supervision of a dentist or physician.

d. *Package limit.* Products containing tinctures of benzoin should be packaged in well-closed containers of 30 mL or less and should have child-proof caps.

2. *Category II conditions under which oral mucosal protectant active ingredients are not generally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC relief of oral discomfort drug products effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

None.

Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of a product are unsupported by scientific data and, in some instances, by sound theoretical reasoning. The Panel concludes that such labeling should be removed from the market.

The Panel considers the following examples of claims to be misleading and unsupported by scientific data:

"Especially soothing after extractions or for minor gum boils."

"Gives quick relief that lasts for hours."

"For fast, temporary relief of minor mouth or gum soreness," This claim is too vague.

"For rapid and effective relief of sore gums."

"Subdues the throbbing ache of sore, swollen gums." Claim is too vague, gums may be infected or a deeper problem may exist.

"Relief of discomfort of minor gum disorders before and after gingivectomy." Gingivectomy should be treated by a dentist.

The Panel considers the following terms to be vague and not definitive of the conditions for which relief is sought: "sore spots," "anti-irritation," "comfortable adjustment," "helps comfortable adjustment," "stops pain," "soothes sore gums," "special," "unaccustomed use," "alleviates pain."

The following claims are for conditions that require advice of a dentist: "gum boils," "gum or gingival inflammation," and "abscesses."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I except as noted for specific pharmacotherapeutic groups.

Category III Active Ingredient

Myrrh, fluidextract

Myrrh, fluidextract. The Panel concludes that there are insufficient data available to permit final classification of the safety and effectiveness of myrrh, fluidextract for OTC use as an oral mucosal protectant for the relief of oral discomfort.

(1) *Safety.* No reports of acute or subacute toxicity of myrrh were found. In a pharmacological study, addition of myrrh to oxygenated Locke solutions containing segments of intestines from rabbits or cats resulted in paralysis of the intestinal muscle (paralysis indicated by relaxation of muscle tonicity, inhibition of contractions, and little or no response to subsequent treatment with pilocarpine) (Ref. 1). Locally, myrrh is reported to be stimulating and for this reason may excite peristalsis if ingested (Refs. 2, 3, 4, and 5). Myrrh has been used as an ingredient in certain cathartic pills, e.g., aloe and myrrh pills. (Ref. 6).

Although reports of hypersensitivity were not found, myrrh and benzoin may be cross-sensitizing. In one report, a 22-year old man developed acute eczematous contact dermatitis 23 days following the application of benzoin tincture to the skin under a plaster cast. In later patch tests, he demonstrated sensitivity to benzoin and cross-sensitivity to myrrh, locust, galbanum, gemboge and olibanum (Refs. 3 and 7).

(2) *Effectiveness.* Myrrh tincture applied locally to mucous membranes of the mouth and throat has been reported to have an astringent action, a stimulating action, or stimulating and protective action (Refs. 2 through 5, and 8). Myrrh has been used in treating various disorders of the mouth and throat including spongy gums, aphthous stomatitis, and ulceration of the mouth and throat (Refs. 2, 3, and 5). In addition to being applied in the form of the tincture, myrrh is sometimes used in mouthwashes and gargles (Refs. 2, 9, and 10).

Protectives should be designed to cover the mucous membranes in order to prevent contact with possible irritants. There are no clinical studies to support the effectiveness of myrrh as a protectant. Myrrh is usually applied locally as an alcoholic solution such as the tincture which contains 83 to 88 percent alcohol. Upon evaporation of the alcohol, a water-insoluble protective coating over the area might be left. However, myrrh is also used in the form of a lotion or gargle, prepared by mixing myrrh tincture with aqueous fluids (Refs. 2, 9, and 10). When the tincture is mixed with aqueous fluids a good portion of the myrrh will precipitate out (Ref. 9). Particulate matter from such a gargle would not serve as a protective. Any benefits would have to be derived from other constituents in the drug.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Apply 0.2 to 0.3 ml myrrh, fluidextract, directly to affected area.

(4) *Labeling.* The Panel recommends the Category I labeling above for oral mucosal protectant active ingredients. (See part V. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that there is insufficient evidence to establish the safety and effectiveness of myrrh, fluidextract, as an oral mucosal protectant. Data to demonstrate safety and effectiveness as an agent for the relief of oral discomfort will be required in accordance with the guidelines set forth below. (See part V. paragraph C. below—Data Required for Evaluation.)

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Category III Labeling

None.

C. Data Required for Evaluation

The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

There are no good, generally accepted protocols for testing an oral mucosal protectant. One of the major factors is that the ingredients in this pharmacologic group can be used for a number of different conditions of different etiology. Industry and FDA must cooperate on developing suitable testing methods.

One of the important indications for the use of a protectant is to protect an area of injury or disease from painful stimuli. Areas ordinarily amenable to such therapy are isolated or discrete areas rather than large areas, as one sees in acute herpetic gingivostomatitis; examples of target areas are isolated herpetic lesions and those of aphthous ulcers which occur singly and at infrequent intervals. Other indications would be allergic reactions, abrasions, burns, and oral wounds of a variety of origins.

A protectant, in any of the above conditions, must shield the area from painful stimuli for a reasonable period of time. The protectant must be easily applied to the involved area, must attach to oral mucous membranes and be resistant to saliva and salivary flow. The painful stimulus which is to be obtunded may arise from either thermal (hot or cold), chemical (acid, base, or other), or physical (abrasive foods) sources.

Although protection from painful stimuli would be one of the best measures of effectiveness, the likelihood of finding a test population with standard lesions, in similar areas, at the same stage of development, is very small. Aphthous ulcers, for example, are painful, last 7 to 10 days, and usually heal uneventfully. The amount of pain gradually decreases from the first day to the 10th day, so that the level of pain response to any stimulus would vary with the state of development, making standardization among subjects very difficult.

In view of these difficulties, methods must be developed to measure by physical means the ability of a protectant to adhere to mucous membranes and to resist solution in and by saliva. Such methods may include the use of fluorescent dyes over a minimum time period as an indicator of penetration and protection. Changes in volume displacement may be a useful indicator.

In addition, since there is very little information on either the safety or the toxicity of myrrh, it is impossible to evaluate the safety of the drug. The manufacturers should, therefore, submit data from controlled studies including:

1. Acute and subacute studies (LD_{50}) in more than one species.

2. Chronic studies involving the addition of myrrh in the diets of experimental animals for periods longer than 60 days.

3. Irritation studies involving the application of myrrh in appropriate concentrations to normal and inflamed or irritated mucosal tissues. Both acute and chronic studies should be performed.

VI. Tooth Desensitizers

A. General Discussionge

Tooth desensitizers are agents used to treat "hypersensitive" (ultrasensitive) dentin. This condition sometimes develops when dentin is exposed to the environment of the oral cavity. The dentin, which contains the sensory mechanism of the tooth, is normally covered by either enamel (crown) or cementum (root). When the latter calcified structures are absent as a result of erosion, abrasion, removal by the dentist, a defect in the tooth, or some other cause, the resultant exposed dentin can become ultrasensitive to various stimuli. Temperature change, mechanical stimuli, and certain chemicals may then induce a painful response. The interpretation of the cause of hypersensitive dentin is complex for several reasons: (1) Dental restorations may transmit temperature changes, (2) carious teeth are sensitive to similar stimuli, and (3) a tooth with pulpal degeneration may be sensitive to temperature changes. The dentist may make the diagnosis of hypersensitive dentin if all carious lesions have received professional treatment, if there are no restorations causing the ultrasensitive response, and if there are no symptoms suggestive of pulpal damage.

Even though the consumer cannot self-diagnose dental hypersensitivity and must obtain professional advice, it is still considered useful by the Panel to have tooth desensitizers available as an OTC product for temporary use until a dentist can be seen or after a dentist has diagnosed dental hypersensitivity. It is estimated that there is a significant target population with hypersensitive dentin which would use an OTC dentifrice for desensitization (Ref. 1). Therefore, the Panel recommends that these products be made available to the public with a warning that unless recommended by a dentist, the products are to be used for not more than 2 weeks. The labeling should include appropriate statements on the dangers of neglecting dental care. (See part VI. paragraph B.1 below—Category I Labeling.)

The problems involved in evaluating dentifrices which make the desensitization claim are manifold. The first problem is that of diagnosis as mentioned above. Second, the problem of the mechanism of action of dentin desensitizers is compounded by the currently limited knowledge of normal dentin sensation. Seltzer (Ref. 2) in 1971 reviewed current hypotheses of dentin sensitivity to thermal, tactile, chemical, and electrical stimuli and concluded that basic mechanisms of dentin sensitivity have not been completely elucidated. Everett, Hall, and Phatak (Refs. 1 and 3) state that while the rationale of desensitization procedures is not fully understood, some agents may depend upon denaturation of the superficial ends of Tomes' fibers or of nerve endings in dentin. Other agents may act by depositing an insoluble substance in the ends of the fibers or nerves and thus may act as a barrier to stimuli and still other agents may act by stimulating irritational dentin formation. It is apparent that evaluation of desensitizing agents must be made, at this time, without complete information on the precise mechanism of action. Third, the task of evaluating desensitizing agents is made difficult by the methods of testing which have been

employed. Both thermoelectric and mechanical stimuli have been used in attempts to objectively measure responses. It has been found in numerous studies that it is difficult to objectively measure the subjective response to pain. Other studies to evaluate dentin desensitizers are based upon the patient's subjective response. Craig (Ref. 4) made a strong point in favor of the latter evaluative method when he found that thermal and mechanical stimuli were so poorly tolerated by patients that it was felt that use of such devices may have resulted in false readings arising from anticipation of discomfort. However, Smith and Ash (Ref. 5) made no mention of lack of cooperation by patients when thermoelectrical and mechanical devices were used to measure responses and further noted no significant correlation between a subject's impression of change in sensitivity and actual change in sensitivity as determined by application of quantitative stimuli. The reporting of the degree of relief of hypersensitivity may be either in the form of improvement versus no improvement or various other qualifying statements such as complete, good, moderate, fair, or poor. Thus, comparisons between various studies are difficult.

It is also important to note that the time-course of studies varies considerably, and some agents appear to be more or less effective depending upon the period of time a patient has been using that particular agent (Ref. 6).

Some identifiable causes of tooth sensitivity which would not be relieved by desensitizing agents include microscopic cracks in teeth, inflammation of the pulp, occlusal trauma (injury due to biting), and recently placed restorations. In cases in which the dentin is definitely exposed, there are still multiple causes for the exposure, such as abrasions caused by toothbrushing or other factors, eroding chemicals, exposure due to periodontal surgery, or defective enamel formation. From these many causes, one would expect different quantitative, as well as qualitative, effects of the desensitizers under different conditions.

In view of this background of confusing data and facts, the Panel does not recommend classifying any ingredients in Category I with a claim for desensitization. Further study of tooth desensitizers is recommended utilizing the guidelines which are discussed later in this document. (See part VI. paragraph C. below—Data Required for Evaluation.)

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B. Categorization of Data

1. *Category I conditions under which tooth desensitizer active ingredients are generally recognized as safe and effective and are not misbranded.* The Panel recommends that the Category I conditions be effective 30 days after the date of publication of the final monograph in the **Federl Register.**

Category I Active Ingredients

None.

Category I Labeling

The Panel recommends the following Category I labeling for tooth desensitizer active ingredients:

a. *Indication.* "To aid in the reduction of painful sensitivity of the teeth to cold, heat, acids, sweets, or contact."

b. *Warnings.* (1) "Do not continue use beyond 2 weeks except under supervision of a dentist."

(2) "Do not swallow."

(3) "Children under 12 years of age should be supervised in the use of this product."

(4) "Sensitive teeth may indicate a serious problem which needs prompt care by a dentist."

(5) "See your dentist as soon as possible whether or not relief is obtained."

c. *Directions.* Apply with a toothbrush at least once a day or as recommended by a dentist or physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician.

2. *Category II conditions under which tooth desensitizer active ingredients are not agenerally recognized as safe and effective or are misbranded.* The Panel recommends that the Category II conditions be eliminated from OTC drug products for the relief of oral discomfort effective 6 months after the date of publication of the final monograph in the **Federal Register.**

Category II Active Ingredients

Sodium fluoride (0.44 percent), strontium chloride, and edentate disodium (in combination)

Sodium fluoride (0.44 percent), strontium chloride, and edetate disodium (in combination). The Panel concludes that the combination of sodium fluoride (0.44 percent), strontium chloride, and edetate disodium is not generally recognized as safe and effective for OTC use as a tooth desensitizer.

In the product submitted, sodium floride and strontium chloride are kept in solution by means of edetate disodium which chelates strontium and prevents formation of insoluble strontium chloride (Ref. 1).

(1) *Safety.* The Panel has recommended 0.22 percent sodium fluordie dentifrice as safe for daily use as an anticaries agent (45 FR 20682; March 28, 1980). The formula submitted has 0.44 percent sodium fluoride (Ref. 1). The Panel considers that the increased amount of fluoride gives an increased risk without proven benefit as a tooth desensitizer. Strontium chloride at 10 percent is considered safe by the Panel.

Edetate disodium has chelating properties (Ref. 2). It is considered unsafe by the Panel for use in OTC dental products because chelating properties may cause decalcification of teeth.

(2) *Effectiveness.* Sodium fluoride at 0.22 percent has been recommended for Category III as a tooth desensitizer. Strontium chloride at 10 percent has also been recommended as a Category III tooth desensitizer. There are no data on effectiveness of the combination formulation other than testimonial letters nor are there any data on the effectiveness of edetate disodium as a tooth desensitizer (Ref. 1).

(3) Labeling. The combination product is currently labeled for use by dentists in the office. The Panel takes no position on this use. Labeling the combination for OTC use would result in misbranding.

(4) *Evaluation.* The Panel considers 0.44 percent sodium fluoride unsafe for OTC use. There are no data to support the effectiveness of the combination. The Panel has serious reservations

about OTC use of sodium edetate. The Panel, therefore, recommends that the combination be classified in Category II.

References

(1) OTC Volume 080010.

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Category II Labeling

The Panel concludes that the use of certain labeling claims related to the safety or effectiveness of a product are unsupported by scientific data and, in some instances, by sound theoretical reasoning. The Panel concludes that such labeling should be removed from the market.

The Panel considers the following examples of claims to be misleading and unsupported by scientific data:

"Gives quick relief that lasts for hours."

"Builds increasing protection against painful sensitivity to cold, heat, sweet, sour, or contact." This claim implies a slow mechanism of action.

The Panel considers that claims which imply a superiority in onset of action, such as "quicker," "more quickly," and "faster," are misleading.

The Panel considers the following terms to be vague and not definitive of the condition for which relief is sought: "anti-irritation," "stops pain," "special," "unaccustomed use," and "alleviates pain."

3. *Category III conditions for which the available data are insufficient to permit final classification at this time.* The Panel recommends that a period of 2 years be permitted for the completion of studies to support the movement of Category III conditions to Category I except as noted for specific pharmacotherapeutic groups.

Category III Active Ingredients

Citric acid and sodium citrate in poloxamer 407 (pluronic F-127™ gel)
Fluoride preparations (sodium fluoride, sodium monofluorophosphate, and stannous fluoride)
Formaldehyde solution
Potassium nitrate
Strontium chloride

a. *Citric acid and sodium citrate in poloxamer 407 (pluronic F-127™ gel).* The Panel concludes that a combination of citric acid and sodium citrate in poloxamer 407 is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC use as a tooth desensitizer for the relief of oral discomfort.

(1) *Safety.* After reviewing the submitted data, the Panel finds that there is a marketing history of the use of citric acid, sodium citrate, and poloxamer 407 as individual ingredients but not as a combination product for use as a tooth desensitizer. Citric acid is used in the food industry in the preparation of fruit juice drinks, carbonate beverages, dairy products, and fruit jellies and preserves. Sodium citrate is used in mouthrinses, ice cream, evaporated milk, and in the curing of certain meats. Poloxamer 407 is used in mouthrinses and as a solubilizing and stabilizing agent in food products (Ref. 1). Based on these data the Panel concludes that there is general recognition of safety.

(2) *Effectiveness.* The Panel concludes that the available data are insufficient to establish general recognition of this combination as effective (Ref. 1).

(3) *Proposed dosage.* Adults and children 2 years of age and older: Brush teeth at least once a day or as recommended by a dentist or physician with 2 percent sodium citrate and citric acid in poloxamer 407 in a suitable dentifrice formulation.

(4) *Labeling.* The Panel recommends the Category I labeling for products containing tooth desensitizer active ingredients. (See part VI. paragraph B.1. above—Category I labeling.)

(5) *Evaluation.* The Panel concludes that the published data on the combination of citric acid and sodium citrate in poloxamer 407 do establish safety, but they are insufficient to establish effectiveness of the combination as a tooth desensitizer. Data to demonstrate effectiveness of this combination as a tooth desensitizer will be required in accordance with the guidelines set forth elsewhere in this document. (See part II. paragraph E.3. above—Testing guidelines for Category III combination products. See also part VI. paragraph C. below—Data Required for Evaluation.)

Reference

(1) OTC Volume 080221.

b. *Fluoride preparations (sodium fluoride, sodium monofluorophosphate, and stannous fluoride).* The Panel concludes that fluoride preparations are safe at the proposed dosages but that there are insufficient data available to permit final classification of their effectiveness for OTC use as tooth desensitizers for the relief of oral discomfort.

(1) *Safety.* The toxicity of fluoride compounds can be attributed to the fluoride ion, which is considered to be protoplasmic poison. Studies of the recorded cases of acute fluoride poisonings indicate that a dose range of 5 to 10 g of sodium fluoride can be considered a lethal dose for a 70-kg man (Refs. 1 and 2).

Much is known of the chronic effects of fluoride because of the widespread use of dietary fluoride in drinking water to provide protection against dental caries. Presently, more than 105 million people in the United States live in areas in which the water supplies contain 0.7 parts per million (ppm) or more fluoride ion, with 94 million of these people receiving water supplemented with additional fluoride to provide a trace level of approximately 1 ppm (Ref. 2). Drinking water having a level of approximately 1 ppm of fluoride will provide a substantial reduction of about 60 percent in the incidence of dental decay without any adverse effect. Dental fluorosis has been reported from daily intake of water with 2 to 10 ppm of fluoride and crippling skeletal fluorosis with levels of 20 to 80 ppm of fluoride in the drinking water (Ref. 3). It should be noted that dental fluorosis occurs only when excessive fluorides are ingested regularly during the period of tooth development.

A number of studies have been conducted, utilizing a variety of testing procedures, to determine the fluoride ingested during toothbrushing with the fluoride-containing dentifrice (Refs. 4 through 9). These studies indicate that, even in children aged 3 to 6 years, the large majority of individuals swallow less than 0.5 g of toothpaste per brushing. The greatest amount swallowed was reported by Hargreaves, Ingram, and Wagg (Ref. 8) as being only slighty over 1 g. If the above information is used when considering a toothpaste formulation containing 0.22 percent sodium fluoride, the amount of fluoride swallowed per average brushing would be 0.25 mg or less. Studies by Ericsson (Ref. 6), Duckworth and Joyston-Bechal (Ref. 10), Barnhart (Ref. 11), and Glass et al. (Ref. 9) all showed the amount swallowed was substantially less than that shown by Hargreaves, Ingram, and Wagg (Refs. 4 and 8). This amount can be considered well below a toxic range.

It is conceivable that a child who regularly swallows excessive amounts of fluoride-containing toothpaste and also consumes fluoridated water could have a total daily fluoride intake in the range that produces dental fluorosis. However, there is a lack of any documentation that dental flurosis has increased significantly following extremely widespread use of fluoride-containing dentifrice for approximately 15 years.

Acute and subacute toxicity studies with sodium monofluorophosphate suggest that the compound on the basis of both milligrams of compound and milligrams of fluorine is less toxic than

sodium fluoride (Refs. 12, 13, and 14). Although the accumulation of fluoride in bone and teeth appears to be similar for sodium monofluorophosphate and sodium fluoride when used at the same fluoride concentration (Ref. 15), studies with radioactive fluoride suggest that the lower toxicity may result from the gradual release of the fluoride ions from the monofluorophosphate (Ref. 16).

Animal feeding studies suggest that the chronic toxicity of sodium monofluorophosphate and sodium fluoride are of the same order and have similar characteristics with the kidney being the most susceptible to pathological change (Ref. 17). Further, the two compounds seem to produce the same degree of mottling in the incisors of albino rats (Ref. 18). When the same quantities of fluoride are given to rats in the form of sodium fluoride, sodium monofluorophosphate , stannous fluoride, and stannous chlorofluoride, similar amounts of fluorine are found in the skeleton (Ref. 19). The monofluorophosphate ion ($PO_3F^=$) also does not appear to pass the placenta to any greater extent than the fluoride ion (Ref. 20).

There is no available information of human toxicity with sodium monofluorophosphate as there is with sodium fluoride. Although acute toxicity of sodium monofluorophosphate in animals is less than that of sodium fluoride, the chronic toxicity is similar. It would, therefore, appear suitable to consider, for human use, that the two compounds have similar toxicity in terms of the fluoride present.

Because stannous fluoride may differ in toxicity from sodium fluoride and sodium monofluorophosphate because of the tin ion, some comments on the acute and chronic toxicity of stannous fluoride may be pertinent. The LD_{50} for mice ingesting stannous fluoride in aqueous solution was found to vary from 169 mg/kg (Ref. 21) to 246 mg/kg (Ref. 22). For rats the LD_{50} was 260 mg/kg (Ref. 21). Levels of stannous fluoride providing up to 18 ppm fluoride in the drinking water or 8 ppm fluoride in the diet for a 140-day period did not inhibit growth or incisor pigmentation in rats. Levels above 9 ppm fluoride in food adversely affected growth and incisor pigmentation and at levels of 150 ppm fluoride some animals died (Ref. 23). Tin from tin salts was reported to have a no-effect level in rats at 22–23 mg/kg and guinea pigs survived on a diet containing 777 ppm tin as tin salt (Ref. 23).

The presence of the stannous ion in stannous fluoride dentifrice formulations may cause some staining of plaque and debris accumulation on the teeth. This has been reported in a number of clinical studies in which an attempt was made to determine the level of staining (Refs. 24, 25, and 26). However, the frequency and intensity of staining with the level of tin present in these formulations does not appear to present any significant problem; therefore, no warning on staining is required for stannous fluoride dentifrice formulations (Ref. 27).

(2) *Effectiveness.* In animal studies, although acute toxicity of sodium monofluorophosphate is less than that of sodium fluoride, the chronic toxicity is similar (Refs. 17, 18, and 20). It would, therefore, appear suitable to consider that the two compounds have similar toxicity for human use. Sodium fluoride, sodium monofluorophosphate, and stannous fluoride have been recommended for Category III as tooth desensitizers. Since the availability of the fluoride ion is similar in all these preparations, it would suggest that the effectiveness data are also related in a similar manner (Ref. 28). The Panel concludes that fluoride-containing dentifrices are safe and effective for OTC use as anticaries agents when marketed in packages containing not more than 260 mg of fluorine, but there are insufficient data to show effectiveness of fluorides as tooth desensitizers at the concentrations permitted in OTC drug products. Effectiveness should be tested for those fluoride compounds that meet the laboratory testing requirements for Category I anticaries fluorides and at the concentrations approved for OTC anticaries use. The laboratory testing requirements recommended by the Panel can be found in the preamble to the proposed monograph on anticaries drug products in the section entitled "Laboratory testing profiles" (45 FR 20677; March 28, 1980).

Kanouse and Ash (Ref. 28) reported favorably on a sodium monofluorophosphate containing dentifrice, but employed a calibrated thermoelectrical device for rating hypersensitivity. Shaprio et al. (Ref. 29) demonstrated reductions in hypersensitivity per individual teeth and per person. Three dentifrices were used, a control, one with sodium monofluorophosphate, and one with strontium chloride. At 4 weeks the reduction with use of the test products was significantly better than the control, but at 8 weeks the difference was no longer apparent. The areas for evaluation were carefully identified and recorded and therefore not blinded. Hernandez et al. (Ref. 30) in a similar study evaluated hypersensitivity at 6 weeks. Hypersensitive areas were not blinded. For a second 6-week period, all three groups (control, sodium monofluorophosphate, and strontium chloride dentifrices) used the control dentifrice. As reported earlier, the net improvement in hypersensitivity for the 12-week control group exceeded the original strontium chloride test group. The Panel felt that additional testing as described below was indicated. (See part VI. paragraph C. below—Data Required for Evaluation.)

In a study designed to evaluate the desensitizing effect of a dentifrice containing 0.76 percent sodium monofluorophosphate, Bolden, Volpe, and King (Ref. 31) included in addition to a nonsodium monofluorophosphate control dentifrice, one with 1.4 percent formalin and one with 0.4 percent stannous fluoride. The sodium monofluorophosphate dentifrice was the superior performer. After 2 weeks the stannous fluoride dentifrice showed the second lowest percent improvement in hypersensitivity. At 4 weeks, it was the lowest of all, including the control. Although a double-blind was established in that neither the examiner nor the patient was aware of the dentifirce assignment, all evaluations were done "in exactly the same anatomical tooth areas that had been previously evaluated" for the baseline data. This procedure may have introduced a potential bias favoring reduction in sensitivity from the use of the "blinded" dentifrices. The Panel felt the areas for evaluation should also be blinded. Hazen, Volpe, and King (Ref. 32), in a duplicate study using the same agents, found stannous fluoride second only to the dentifrice with sodium monofluorophosphate in its ability to reduce hypersensitivity in teeth. The evaluation of hypersensitive areas was not blinded.

Miller et al. (Ref. 33) in a double-blind crossover study reported improvement in hypersensitivity in 20 of 23 patients with the use of a water-free stannous fluoride-containing gel. Hypersensitive areas were not blinded, nor were the specific measures used to evaluate changes in sensitivity described. The Panel felt that additional testing as described below was indicated. (See part VI. paragraph C. below—Data Required for Evaluation.)

(4) *Proposed dosage.* Adults and children 2 years of age and older: Brush teeth at least once a day or as recommended by a dentist or physician with 0.22 percent sodium fluoride, 0.76 percent sodium monofluorophosphate, or 0.4 percent stannous fluoride in a suitable dentifrice formulation.

(5) *Labeling.* The Panel recommends the Category I labeling for products containing tooth desensitizer active ingredients. (See part VI. paragraph B.1. above—Category I Labeling.)

In addition, fluoride-containing dentifrices should not contain more than 260 mg total fluorine.

(6) *Evaluation.* The Panel concludes that OTC Category I anticaries fluoride dentifrices are Category III with respect to claims as tooth desensitizing agents. The Panel concludes that fluoride dentifrices are safe at the proposed dosage, but there is insufficient evidence to establish effectiveness as tooth desensitizing agents. Data to demonstrate effectiveness as a tooth desensitizer will be required in accordance with the guidelines set forth below. (See part VI. paragraph C. below—Data Required for Evaluation.)

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c. *Formaldehyde solution.* The Panel concludes that 1.4 percent (w/w) formaldehyde solution is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC use as a tooth desensitizer for the relief of oral discomfort.

(1) *Safety.* Clinical use and marketing experience have confirmed that 1.4 percent (w/w) of formaldehyde solution is safe for OTC use.

Formaldehyde solution is an aqueous solution containing approximately 40 percent weight to volume of formaldehyde gas with methanol added as a preservative. Formaldehyde solution is clear and colorless and has a pungent odor. The solution is incompatible with oxidizing agents and with alkali (Ref. 1).

Contact with formaldehyde solutions may lead to dermatitis producing reddening, inflammation, and necrosis if applied repeatedly by allergic or sensitive individuals (Refs. 1 and 2). A manufacturer of a 1.4-percent (w/w) formaldehyde solution-containing dentifrice reported a low incidence of consumer complaints of mouth reactions or gingival injuries from the use of this product (Ref. 3).

(2) *Effectiveness.* Although formaldehyde solution has been used for the relief of pain due to hypersensitive teeth, its effectiveness in a dentifrice for desensitizing has not been conclusive. In one study, 20 patients were selected on the basis of cervical hypersensitivity and evaluated by application of mechanical and thermal (heat and cold) stimuli (Ref. 4). Subjects were advised to brush with the dentifrice at least once daily or as many times a day as they did prior to use of the dentifrice. This study was of controlled, crossover design. At the end of a 30-day treatment period the placebo group was switched to the treatment dentifrice, and the original treatment group was continued for an additional 30 days. The conclusion was that there was no significant alteration

of cervical hypersensitivity to mechanical or thermal stimuli after use of this product for 30 or 60 days.

In another study 72 adults, all having a history of dental hypersensitivity, were selected for treatment of chronic periodontitis (Ref. 5). Forty-seven patients were instructed to brush after each meal with a desensitizing tooth paste. Twenty-four patients were placed in a placebo group using a control dentrifice. The patients used one of the dentifrices for 5 weeks during which time they received periodontal therapy (root planing and gingivectomy). This was a double-blind, subjective evaluation with no statistical analysis. The conclusion was that the product may be of some value for patients undergoing periodontal therapy.

When a formaldehyde solution-containing dentifrice was compared with one containing sodium monofluorophosphate, the desensitizing effectiveness of 1.4 percent formaldehyde was not as great as that of the sodium monofluorophosphate dentifrice (23.5 percent vs. 29.2 percent) after 2 weeks of treatment, but was slightly better than the control (50.6 percent vs. 46.0 percent) after 4 weeks of treatment (Ref. 6). These differences are not statistically significant. Another study compared sodium monofluorophosphate, a control dentifrice without sodium monofluorophosphate, and a 1.4 percent formaldehyde dentifrice. At the end of 4 weeks the control dentifrice without sodium monofluorophosphate provided 38 percent reduction of sensitivity, and the formaldehyde-containing dentifrice provided a 33.8-percent reduction. These reductions were not statistically different from each other (Ref. 7).

Several other studies gave ambiguous results (Refs. 8 through 11). Although the use of a formaldehyde-containing dentifrice appeared to give favorable results in some instances, basic defects in experimental design or lack of statistical significance left doubts concerning the effectiveness of the product.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Brush teeth at least once a day or as recommended by a dentist or physician with 1.4 percent (w/w) formaldehyde solution in a suitable dentifrice formulation.

(4) *Labeling.* The Panel recommends the Category I labeling for tooth desensitizer active ingredients. (See part VI. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that there is insufficient information to establish the effectiveness of 1.4 percent (w/w) formaldehyde solution in a suitable dentifrice formulation as a tooth desensitizer. Data to demonstrate effectiveness as a tooth desensitizer will be required in accordance with the guidelines set forth below. (See part VI. paragraph C. below—Data Required for Evaluation.)

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d. *Potassium nitrate.* The Panel concludes that 5 percent potassium nitrate is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC use as a tooth desensitizer for the relief of oral discomfort.

(1) *Safety.* Nitrates are components of the normal environment. Soil bacteria are principally responsible for their presence, although compounds of nitrogen, during transport in the air, can be oxidized to nitrates. Large deposits of nitrate salts formed in this way exist in various locations on the earth.

Nitrates in the soil are the primary source of fixed nitrogen for green plants. A second source is ammonia in the soil, either from natural (bacterial action on dead plant or animal matter) or synthetic (applied fertilizer) sources. Nitrates are absorbed and may accumulate in plants at high levels, especially if the soil is rich in nitrates. Some vegetables, notably lettuce, beets, celery, radishes, and spinach contain substantial quantities of nitrates. An estimated average per capita daily ingestion of nitrate in the United States is 86 mg. This comes principally from vegetables but there is a great variation in intake depending upon the type and quantity of the vegetables consumed and the condition of the soil in which the vegetables were grown. Until elimination, cheifly via the urine, nitrate is recycled by secretion in the saliva. The nitrate-to-nitrite conversion does not take place in the 5-percent dentifrice product which was submitted to the Panel (Ref. 1). No known toxic effects are produced in man in doses of 1 to 1.5 g potassium nitrate. In light of the estimated dietary intake of nitrates (86 mg) and the relatively small amount (30 mg) available for ingestion from the use of a toothpaste, the Panel concludes that no toxicological hazard exists from use of a dentifrice with potassium nitrate at the 5-percent level.

(2) *Effectiveness.* Two published studies and two unpublished studies are reviewed below (Refs. 1 through 4). Among these four studies only limited data are presented on the 5-percent potassium nitrate toothpaste. In some instances the findings are conflicting and are always based on very small samples of persons and teeth. An 8.5-percent potassium nitrate dental prophylaxis paste available OTC has been promoted to the dental profession for office use since 1974 (Ref. 1). The Panel agreed that the marketing experience data concerning this product could not be substituted for marketing experience with an OTC dentifrice intended for use at home. The Hodosh study (Ref. 2) described this positive effect of potassium nitrate in solutions of 15, 10, 5, 2, and 1 percent when painted on hypersensitive teeth. A 10-percent potassium nitrate paste for office use was also reported. Only 35 patients used the home dentifrice (10 percent potassium nitrate by weight), but positive results were reported. However, no controls were used, no system of evaluation was described, and no statistical analysis was included.

In a report of Stark et al. (Ref. 3), on a new device for testing sensitivity, a potassium nitrate dentifrice was used successfully by 10 patients. The primary purpose of this study was to compare findings of a new electric pulp test against conventional pulp testers. The concentration of potassium nitrate in the dentifrice was not stated. Additional

study of the data reported by Stark et al. (Ref. 3) disclosed that for one group (five persons, but only three with hypersensitive teeth) a significant reduction in hypersensitivity was found immediately after application of the potassium nitrate (5-percent solution). This is contrary to Starks' published findings (Ref. 3), where there was little or no immediate reduction in sensitivity. Seven days later, sensitivity was rated again and a paste containing 5 percent potassium nitrate in kaolin and glycerin paste was burnished by the dentist against the cervical area of the teeth. Reduction in hypersensitivity was maintained at each assessment. Normal oral hygiene including brushing with a dentifrice without a desensitizing agent was followed throughout the study (Ref. 3).

In a second unpublished study potassium nitrate at 5 and 10 percent in home-use dentifrices was compared with a single application of sodium fluoride, 33⅓ percent, in a kaolin and glycerin burnishing paste (Ref. 1). The study groups were composed of 7, 14, and 6 persons, respectively. Immediate reduction in sensitivity was significant with the burnished fluoride paste but not with potassium nitrate toothpastes. Significant reduction was reported at 1 week for the 10-percent potassium nitrate paste and at 2 weeks for both the 5-percent and 10-percent pastes.

Three additional unpublished studies, one evaluating a test procedure and two others presenting data on potassium nitrate, were submitted to the Panel for review (Ref. 4). The first compares the pulp stethoscope with cold air as a procedure for evaluating hypersensitivity. The data suggest that the two test procedures are assessing the various levels of sensitivity in a comparable manner. The two other studies present data on the use of potassium nitrate in a desensitizer dentifrice. The findings indicate that the potassium nitrate dentifrice may be effective in reducing sensitivity, but the evidence is not convincing. The test groups were somewhat small in number and, in several, the levels of initial hypersensitivity were very low.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Brush teeth at least once a day or as recommended by a dentist or physician with 5 percent potassium nitrate in a suitable dentifrice dosage form.

(4) *Labeling.* The Panel recommends the Category I labeling for tooth densensitizer active ingredients. (See part VI. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that 5 percent potassium nitrate is safe but that there are insufficient data to establish effectiveness of 5 percent potassium nitrate in a suitable dentrifice formulation as a tooth densensitizer. Although the product is available without a prescription, marketing experience has been limited to use by professionals in the dental office. Data to demonstrate effectiveness as a tooth densensitizer will be required in accordancewith the guidelines set forth below. (See part VI. paragraph C. below—Data Required for Evaluation.)

References

(1) OTC Volume 080229.

(2) Hodosh, M., "A Superior Densensitizer—Potassium Nitrate," *Journal of the American Dental Association*, 88:831–832, 1974.

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(4) OTC Volume 080259.

e. *Strontium chloride.* The Panel concludes that 10 percent strontium chloride is safe but that there are insufficient data available to permit final classification of its effectiveness for OTC use as a tooth desensitizer for the relief of oral discomfort.

(1) *Safety.* Animal studies have clearly shown that some strontium compounds are tolerated in what could be considered large amounts (Refs. 1 through 4). There is general agreement that strontium chloride hexahydrate is no more and may even be less toxic than calcium (Refs. 1, 3, 10, and 11). Reports on strontium chloride hexahydrate are limited, but are consistent in that safety does not appear to be a problem (Refs. 2 and 3). Industry-sponsored studies of strontium chloride hexahydrate at 10 percent by weight in a dentifrice produced no measurable toxic reactions (Ref. 5).

The metabolism of strontium resembles very closely that of calcium, especially with regard to developing bone and teeth (Ref. 6). Interest in its behavior as a radioactive isotope, strontium 90, heightened in recent years since it is a constituent of the fallout from atomic weapon testing (Refs. 6 and 7). The consequent hazard from the accumulation of the isotope in bones and teeth drew much attention.

One review of the toxicity of strontium states that no threshold values for human toxicity have been reported by any official agency in the United States (Ref. 7). Strontium chloride hexahydrate, present at 10 percent by weight in a toothpaste, has been marketed for 12 years with no report of adverse reactions (Ref. 5). Published clinical studies contain no reports of adverse reactions (Refs. 10 through 13). The Panel agreed that strontium chloride as the hexahydrate appears to be safe for OTC use in a dentifrice at a concentration of 10 percent.

(2) *Effectiveness.* The Panel found that the reported findings from various clinical trials of dentifrices containing strontium chloride were both conflicting and inconclusive. The required time for reducing sensitivity has been variously reported at 3 days and 20 days by Pusso-Carrasco (Ref. 11), at 6 weeks by Hernandez et al. (Ref. 14), and at 4- and 8-week periods by Shapiro et al. (Ref. 15).

Hernandez et al. (Ref. 14), after a 6-week evaluation, placed the two test groups (sodium monoflurophosphate and strontium chloride) on the control dentifrice and continued the original control group on the control dentifrice for an additional 6 weeks. Both test groups lost some of the improvement in hypersensitivity gained during the first 6 weeks. The control group improved remarkably during the second 6-week period to a level slightly better than the test group formerly using the strontium chloride dentifrice.

An unpublished study conducted at the Osaka University Dental School, Osaka, Japan (Ref. 16), was submitted to the Panel for review. A unique and surprising result of this study was very low response to the placebo product.

In a well-controlled, double-blinded clinical trial reported by Graf (Ref. 17), both the test group and the control group showed measurable reduction in hypersensitivity at 4, 8, and 12 weeks. The difference between the test and control groups was not statistically significant, however. In a second attempt, Graf (Ref. 17) found similar results at 3 months and not until 6 months could a statistical significance be established between test and control group reductions in hypersensitivity. The lack of early, consistent, favorable, and statistically significant results from clinical studies left the Panel with many doubts about the effectiveness of strontum chloride as an agent for the reduction of dental hypersensitivity.

(3) *Proposed dosage.* Adults and children 2 years of age and older: Brush teeth at least once a day or as recommended by a dentist or physician with 10 percent strontium chloride in a suitable dentifrice formulation.

(4) *Labeling.* The Panel recommends the Category I labeling for tooth desensitizer active igredients. (See part VI. paragraph B.1. above—Category I Labeling.)

(5) *Evaluation.* The Panel concludes that 10 percent strontium chloride is safe but that there are insufficient data to establish the effectiveness of 10 percent strontium chloride in a suitable dentifrice formulation as a tooth desensitizer. Data to demonstrate effectiveness as a tooth desensitizer will be required in accordance with the guidelines set forth below. (See part VI. paragraph C. below—Data Required for Evaluation.)

References

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(5) OTC Volume 080033.

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(8) Osol, A., et al., "The Dispensatory of the United States of America, 25th Ed., J. B. Lippincott Co., Philadelphia, p. 1872, 1955.

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(16) OTC Volume 080257.

(17) Graf, H., "Sensodyne Clinical Trials," draft of unpublished study incorporated in OTC Volume 080224.

Category III Labeling

None.

C. Data Required for Evaluation.

The Panel has agreed that the guidelines recommended in this document for the studies required to bring a Category III drug into Category I are in keeping with the present state of the art and do not preclude the use of any advances or improved methodology in the future.

1. *General principles in the design of an experimental protocol for testing tooth desensitizers.* Three independent investigations will be required. An academic setting for the studies seems most appropriate since most private offices and clinics would have neither the facilities nor the volume of patients necessary for the projects.

Monitoring of the studies should be as complete as possible. Placebo samples must be indistinguishable from test samples with regard to taste, consistency, and appearance. The abrasive in the test product should be the same as that used in the placebo. Both test and placebo samples should be assigned random numbers and the code should not be broken until the completion of the study. Data may be evaluated by sequential analysis of paired test and placebo trials. This seems to be the most efficient methodology, but other recognized and accepted study designs and statistical analyses are acceptable. The two criteria for change in sensitivity described later must be met for an active ingredient to be considered effective.

2. *Selection of patients.* At an initial screening, selected patients should complain of hypersensitive teeth (or tooth) limited to either or both of the following types: (1) Postperiodontal surgery (6 weeks minimum) (Type I), and (2) cervical erosion, abrasion, or exposed dentin resulting from gingival recession (Type II).

All other types of hypersensitivity should be rejected.

Each of the investigations should include persons with the same type of sensitivity (as described above). Among the three investigations, at least one must be on persons with Type I sensitivity.

Persons selected for test and placebo trials should be of the same sex and reasonably similar in age, in number of hypersensitive teeth, and in the mean sensitivity score. Appropriate release forms should be completed, and institutional approval for human experimentation must be given.

Teeth which may be included in the study are the incisors, canines, and premolars in both arches.

3. *Study method.* In the case of postperiodontal surgery, Type I sensitivity, rating the sensitivity of an interproximal space of two adjacent teeth is not acceptable. The facial surface of the individual tooth is the assessment unit.

For persons with Type II sensitivity, sensitivity will be rated on the facial surface of all teeth present in both jaws except those teeth with pulpitis, cracked enamel, or fillings on some part of the facial surface. Rating all teeth will additionally blind the examiner and the study person. Ratings will be done on individual teeth isolated from adjacent teeth mesially and distally by the examiners' fingers, cotton rolls, or some other appropriate device.

The use of tactile stimulation as a method of evaluating tooth hypersensitivity has been traditional. It is a very familiar clinical procedure to most practicing dentists. Difficulties have been encountered by many researchers in establishing a standardized tactile procedure and in assessing the degree of standardization either among examiners at a point in time or within the same examiner over time. Therefore, other assessment procedures have been sought which have more obvious and measurable levels of reliability. The Panel encourages the further development and use of these improved procedures. The use of tactile stimulation for the evaluation of tooth hypersensitivity is acceptable but is not encouraged.

The sensitivity rating will be the subjective response of the study person to a standardized thermal stimulus according to the following scale:

0=no significant discomfort, aware of stimulus
1=discomfort but no severe pain
2=severe pain during application of stimulus
3=severe pain during and continuing after application of stimulus

One of the following standardized stimulus mechanisms may be used:

(1) 1 second or less of cold air from the air syringe making certain that the time and the air temperature and pressure are standardized for each rating.

(2) 0.2 mL of ice water on an isolated surface making certain that the time and temperature are standardized for each rating.

(3) Selected levels applied by the thermoelectric stimulator described by Smith and Ash (Ref. 1).

(4) Electrical stimulation with microcurrents at variable levels.

(5) Tactile stimulation by the dental explorer for a stated time interval and at a standard pressure.

The reduction in hypersensitivity will be measured by comparing the mean sensitivity scores at the initiation of the investigation with the mean scores at the various test intervals.

Mean sensitivity score-*initial*=Summation of 1, 2, 3 ratings divided by number of teeth so rated (exclude 0-rated teeth).

Mean sensitivity score-*test interval*=Summation of all ratings for teeth included in initial mean score divided by number of teeth scored (include 0-rated teeth).

Following the initial sensitivity ratings, evaluation for sensitivity should be completed at 2-week, 4-week, and 8-week intervals. Additional evaluations at 4 and 6 months, although not recommended by the Panel, are optional.

4. *Interpretation of data.* If sequential trial charts are used, they will be completed at the end of the 8-week trial without a break in the coding during the period. (Those persons on placebo who claim no relief of pain should be treated for hypersensitivity following the test period.) Assessment of paired sample persons will be made at the 2-, 4-, and 8-week periods.

In determining the boundaries for the analysis chart, the probabilities of errors should range from 5 to 10 percent. Paired sample persons will be entered on the analysis chart only when the active ingredient has demonstrated a reduction of 33 percent or greater in the initial mean sensitivity score. A favorable placement on the chart will be made when the active ingredient shows a 50-percent greater reduction in the mean sensitivity score than the placebo reduction.

Regardless of the study design or the statistical analysis employed, to be considered effective, the active ingredient must demonstrate the above-stated requirements, i.e., 33-percent or greater reduction in the initial mean sensitivity score and a 50-percent greater reduction than the placebo reduction.

Example first paired sample persons:

	Mean sensitivity scores	
	Active	Placebo
Initial Mean	2.5	2.4
2 Week Mean	1.5	2.0
Percent Reduction	40	17

A 40-percent reduction is greater than 33 percent; therefore, the paired sample is eligible for the analysis chart. A favorable placement on the chart is indicated since the 40-percent reduction for the active is more than 50 percent greater than the 17-percent reduction for the placebo.

The Panel has agreed that 3 years after the publication of the proposed rules is an adequate time period for completion and submission of data for these studies.

Reference

(1) Smith, B. A., and M. M. Ash, "Evaluation of a Desensitizing Dentifrice," *Journal of the American Dental Association*, 68:639–647, 1964.

List of Subjects in 21 CFR Part 354

Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704)), and under 21 CFR 5.11 as revised (see 47 FR 16010; April 14, 1982), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding new Part 354, to read as follows:

PART 354—DRUG PRODUCTS FOR THE RELIEF OF ORAL DISCOMFORT FOR OVER-THE-COUNTER HUMAN USE

Subpart A—General Provisions

Sec.

Subpart B—Active Ingredients

Subpart C—[Reserved]

Subpart D—Labeling

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

Subpart A—General Provisions

§ 354.1 Scope.

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

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

§ 354.3 Definitions.

As used in this part:

(a) *Agent for the relief of oral discomfort.* An ingredient which when applied topically has direct or indirect capability to relieve oral discomfort. This category of drugs includes oral mucosal analgesics, tooth desensitizers, oral mucosal protectants, and agents for the relief of toothache.

(b) *Agent for the relief of toothache.* An ingredient used for the temporary relief of pain arising as a result of an open tooth cavity.

(c) *Oral mucosal analgesic.* An ingredient used in dental care drug products for topical application in the oral cavity to provide temporary relief of oral discomfort by an anesthetic or analgesic effect.

(d) *Oral mucosal protectant.* An ingredient which is a pharmacologically inert substance which forms an adherent, continuous, flexible, or semirigid coating when applied to the oral mucous membranes. The coating protects the irritated area from further irritation due to the activity of oral structures.

(e) *Tooth desensitizer.* An ingredient which acts on the dentin to block perception of those stimuli which are usually not perceived by normal subjects but which are perceived by patients with dental hypersensitivity.

Subpart B—Active Ingredients.

§ 354.10 Agents for the relief of toothache.

The active ingredient of the product may consist of the following when used within the dosage limit established: Eugenol 85 to 87 percent.

§ 354.12 Oral mucosal analgesics.

The active ingredients of the product may consist of any of the following

when used within the dosage limits established for each ingredient:

(a) Benzocaine 5 to 20 percent.

(b) Butacaine sulfate 4 percent.

(c) Phenol preparations (phenol and phenolate sodium) 0.25 to 1.5 percent.

§ 354.14 Oral mucosal protectants.

The active ingredient of the product may consist of any of the following when used within the dosage limits established for each ingredient:

Benzoin preparations. (a) Compound benzoin tincture, USP XIX.

(b) Benzoin tincture, USP XV.

§ 354.16 Tooth desensitizers. [Reserved]

§ 354.18 Package size limitations.

(a) Products containing butacaine sulfate identified in § 354.12(b) should be packaged in single-use units to contain no more than 30 milligrams each with no more than six units per package.

(b) Products containing benzoin preparations identified in § 354.14 should be packaged in well-closed containers in a quantity of 30 milliliters or less.

§ 354.20 Permitted combinations of active ingredients.

(a) Any single oral mucosal protectant active ingredient identified in § 354.14 may be combined with any single oral mucosal analgesic active ingredient identified in § 354.12.

(b) Any single oral mucosal protectant active ingredient identified in § 354.14 may be combined with any generally recognized safe and effective oral antiseptic.

(c) Any single oral mucosal analgesic active ingredient identified in § 354.12 may be combined with any generally recognized safe and effective oral antiseptic.

(d) Any single oral mucosal protectant active ingredient identified in § 354.14 and any single oral mucosal analgesic active ingredient identified in § 354.12 may be combined with any generally recognized safe and effective oral antiseptic.

(e) Any single oral mucosal analgesic active ingredient identified in § 354.12 may be combined with any generally recognized safe and effective denture adhesive.

Subpart C [Reserved]

Subpart D—Labeling

§ 354.50 Labeling of agents for the relief of toothache 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 "agent for the relief of toothache."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the phrase "for the temporary relief of throbbing, persistent toothache due to a cavity until a dentist can be seen."

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

(1) *For products containing any ingredient identified in § 354.10.* (i) "Use only in teeth with persistent, throbbing pain."

(ii) "Not to be used for a period exceeding 7 days."

(iii) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(iv) "Do not swallow."

(v) "Do not exceed recommended dosage."

(vi) "Children under 12 years of age should be supervised in the use of this product."

(vii) "A dentist must be seen as soon as possible whether or not the paid is relieved."

(viii) "Toothaches and open cavities indicate serious problems which need prompt attention by a dentist."

(2) *For products containing eugenol identified in § 354.10.* "Do not use if you are allergic to eugenol."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": "Rinse the tooth with water to remove any food particles from the cavity. Moisten a cotton pledget with 1 or 2 drops of medication and place in the cavity for approximately 1 minute. Avoid touching tissues other than the tooth cavity. Apply the dose not more than four times daily or as directed by a dentist or physician. Children 2 to 12 years of age should be supervised in the use of this product. For children under 2 years of age, there is no recommended dosage except under the advice and supervision of a dentist or physician."

§ 354.55 Labeling of oral mucosal analgesic 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 mucosal analgesic."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following:

(1) *For products containing any ingredient identified in § 354.12.* (i) "For the temporary relief of pain due to minor irritation or injury of soft tissue of the mouth."

(ii) "For the temporary relief of pain due to minor dental procedures."

(iii) "For the temporary relief of pain due to minor irritation of soft tissues caused by dentures or orthodontic appliances."

(iv) "For the temporary relief of pain due to recurring canker sores when the condition has been previously diagnosed by a dentist."

(2) *For products containing benzocaine identified in § 354.12(a) or phenol identified in § 354.12(c) when used as oral mucosal analgesics for teething pain.* "For the temporary relief of sore gums due to teething in infants and children 4 months of age and older."

(3) *For products containing any ingredient identified in § 354.12 when used in denture adhesive products.* "For the temporary relief of pain or discomfort of oral tissues due to dentures."

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

(1) *For products containing any ingredient identified in § 354.12.* (i) "Not to be used for a period exceeding 7 days."

(ii) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(iii) "Do not swallow."

(iv) "Do not exceed recommended dosage."

(2) *For products containing any ingredient identified in §§ 354.12 (a) and (c).* "Children under 12 years of age should be supervised in the use of this product."

(3) *For products containing "caine" derivatives identified in §§ 354.12 (a) and (b).* "Do not use this product if you have a history of allergy to local anesthetics such as procaine, butacaine, benzocaine, or other 'caine' anesthetics."

(4) *For products containing butacaine sulfate identified in § 354.12(b).* (i) "Do not use in children under 12 years of age unless recommended by a dentist or physician."

(ii) "Do not use more than one unit at a time."

(iii) "Do not repeat except after 3 hours."

(iv) "Do not exceed 3 doses daily."

(5) *For products labeled with the indication identified in § 354.55(b)(2).* "Fever and nasal congestion are not symptoms of teething and may indicate

the presence of infection. If these symptoms persist, consult your physician."

(6) *For products containing any ingredient identified in § 354.12 when used in denture adhesive products.* "See your dentist as soon as possible."

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

(1) *For products containing benzocaine identified in § 354.12(a).* "Apply to the affected area not more than four times daily or as directed by a dentist or physician. For infants under 4 months of age there is no recommended dosage or treatment except under the advice and supervision of a dentist or physician."

(2) *For products containing butacaine sulfate identified in § 354.12(b).* "Apply to the affected area. Do not use more than one unit at a time (each unit to contain no more than 30 milligrams butacaine sulfate). Do not apply more often than every 3 hours. Do not exceed three applications (90 milligrams) daily. Children under 12 years of age should not use this product except under the advice and supervision of a dentist or physician."

(3) *For products containing phenol identified in § 354.12(c) when used as teething preparations.* "Apply to the affected area not more than six times daily. For infants under 4 months of age, there is no recommended dosage except under the advice and supervision of a dentist or physician." For infants and children 4 months to under 12 years of age, dosage should not exceed 300 milligrams of phenol per day.

(4) *For products containing phenol identified in § 354.12(c) when used as a dental rinse.* "Rinse the affected area not more than six times daily. For children under 6 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician." For adults and children 12 years of age and older, dosage should not exceed 600 milligrams of phenol per day. For children 6 to under 12 years of age, dosage should not exceed 300 milligrams of phenol per day.

(5) *For products containing any ingredient identified in § 354.12 when used in denture adhesive products.* "Apply on area of denture that comes in contact with sore gums."

§ 354.60 Labeling of oral mucosal protectant 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 mucosal protectant."

(b) *Indications.* The labeling of the product contains a statement of the indications under the heading "Indications" that is limited to the following:

(1) "Forms a coating over a wound."

(2) "Protects against further irritation."

(3) "For temporary use to protect wounds caused by minor irritations or injury."

(4) "For protecting recurring canker sores when the condition has been previously diagnosed by a dentist."

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

(1) "Not to be used for a period exceeding 7 days."

(2) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(3) "Do not swallow."

(4) "Do not exceed recommended dosage."

(5) "Children under 12 years of age should be supervised in the use of this product."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": "For adults and children 6 months of age and older: Dry the affected area, saturate a cotton applicator with medication, and apply undiluted to the affected area not more often than every 2 hours. For children under 6 months of age, there is no recommended dosage except under the advice and supervision of a dentist or physician."

§ 354.65 Labeling of tooth desensitizer drug products.

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

(b) *Indications.* The labeling of the product contains a statement under the heading "Indications" that is limited to the phrase "to aid in the reduction of painful sensitivity of the teeth to cold, heat, acids, sweets, or contact."

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

(1) "Do not continue use beyond 2 weeks except under supervision of a dentist."

(2) "Do not swallow."

(3) "Children under 12 years of age should be supervised in the use of this product."

(4) "Sensitive teeth may indicate a serious problem which needs prompt care by a dentist."

(5) "See your dentist as soon as possible whether or not relief is obtained."

(6) "If irritation persists, inflammation develops, or if fever and infection develop, discontinue use and see your dentist or physician promptly."

(7) "Do not exceed recommended dosage."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions": "Apply with a toothbrush at least once a day or as recommended by a dentist or physician. Children under 12 years of age should be supervised in the use of this product. For children under 2 years of age there is no recommended dosage except under the advice and supervision of a dentist or physician."

Interested persons may, on or before August 23, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before September 22, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: March 31, 1982.

Mark Novitch,

Acting Commissioner of Food and Drugs.

Dated: May 13, 1982.

Richard S. Schweiker,

Secretary of Health and Human Services.

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