



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

JAN 8 2002

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R. William Soller, Ph.D.
Senior Vice President and
.Director of Science and Technology
Consumer Healthcare Products Association
1150 Connecticut Avenue, N.W.
Washington, D.C. 20036

Re: Docket No. 81N-0033
Comment No. PR5

Dear Dr. Soller:

This letter is in response to your letter dated April 22, 1999 and coded PR5 under docket number 81N-0033 in FDA's Dockets Management Branch, which responds to agency comments in a letter dated July 17, 1998. Your letter includes a single protocol for a randomized, double-blind, placebo-controlled study in 200 subjects entitled "Evaluation of the Efficacy of 20 Percent Benzocaine for Relief of Toothache."

The same protocol will be used to evaluate the effectiveness of 10 and 20 percent benzocaine in separate studies, as well as 85 percent eugenol. The protocol is designed to determine: (1) The percentage of subjects who experience improvement in their pain score as measured by the predefined 4-point categorical dental pain scale, (2) onset time to meaningful pain relief, and (3) the duration of meaningful relief among all subjects.

In addition, your letter states that you plan to submit information on labeling issues and a summary of safety information relating to benzocaine upon completion of these studies.

We have the following comments:

1. The protocol is not adequate to demonstrate that eugenol can be used safely and effectively in an over-the-counter (OTC) setting. Although the Advisory Review Panel on OTC Dentifrice and Dental Care Drug Products (the Panel) acknowledged that well-controlled studies of the effectiveness of eugenol were not available, it classified

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eugenol (85 to 87 percent) in Category I (generally recognized as safe and effective) for the relief of toothache (47 FR 22712 at 22727, May 25, 1982). The Panel noted, however, that eugenol can damage the pulp of a vital tooth and should only be used in teeth with persistent throbbing pain (indicating irreparable pulpal damage). The Panel believed that, with adequate labeling, consumers could understand that the product should be used only for severe, persistent toothache. However, the agency disagreed with the Panel's Category I classification and placed eugenol in Category III (insufficient data to demonstrate effectiveness) in the proposed rule (56 FR 48302 at 48336, September 24, 1991).

2. It is our opinion that the available published literature does not support the safety of eugenol for OTC use in toothache relief. Based on the Panel's concerns and a review of published literature, there is strong evidence that use of 85 percent eugenol liquid can cause irreversible pulpal damage if placed in a vital tooth (Refs. 1 to 12). Although toxic levels of eugenol cannot further harm an irreversibly damaged pulp, it is unlikely that consumers can correctly determine this condition, or that they would always adhere to label warnings about restricting use of the drug to a tooth having severe and persistent pain. Therefore, the agency has concerns about the safety of using eugenol in an OTC setting.

3. In addition to data demonstrating the effectiveness of eugenol for toothache relief, data from an actual use trial demonstrating that a consumer can understand how and when to use eugenol without the risk of significant toxicity (pulpitis and pulpal necrosis) is needed for a Category I classification to be considered for this ingredient. Further, the study would need to demonstrate that a consumer can: (1) Accurately distinguish a vital tooth from a non-vital tooth, (2) apply eugenol without assistance from a dental professional, and (3) understand when to seek dental intervention. Without such data, we will not have enough evidence to include eugenol in the final monograph.

4. As benzocaine's effect is self-limited and not known to result in significant pulpal damage, a double-blind study of the type described by this protocol is appropriate. However, some of the problems identified in earlier

protocol submissions have not been addressed and should be considered.

5. Although the protocol is designed to show that benzocaine can be used safely under professional supervision, it is not designed to assess consumer understanding or actual use of the product. Information showing that consumers understand how to use benzocaine for toothache relief in an OTC setting should be provided.

6. The protocol does not specify the frequency of dosing (reapplication). Because it is likely that consumers will use the product more than once during an episode of tooth pain, multiple dosing should be assessed. In addition, the study should assess the amount of product necessary to achieve the desired effect and the duration of effect, because these variables will affect dosing instructions.

7. The use of subjects with varying degrees of pain (defined as intensity and frequency) will make it difficult to determine the actual benefit of benzocaine. Because of concern about the high placebo response demonstrated in previous studies, the agency recommended that only individuals with severe pain be included so that the study can show a significant improvement with benzocaine compared to placebo. In addition, the agency recommended that a "responder" be defined as a subject who achieves a 2-point improvement on the pain relief scale. Because these recommendations were not incorporated into the protocol, the agency remains concerned about the ability of this study to show that benzocaine is significantly more effective than placebo. Further, the current protocol specifies a 1-point improvement at any two time points between 5 and 20 minutes. However, because a 1-point difference on the dental pain scale from severe pain to moderate pain (3 to 2) does not have the same implication as a 1-point difference from moderate pain to mild pain (2 to 1), improvement should be identified as either pain "relief" (no toothache pain) or pain "reduction" (pain reduced to mild level on the pain scale proposed) for two consecutive time points.

8. Meaningful relief (secondary effectiveness parameter) and duration of relief should be defined. In addition, the statistical test methods, power calculations to determine

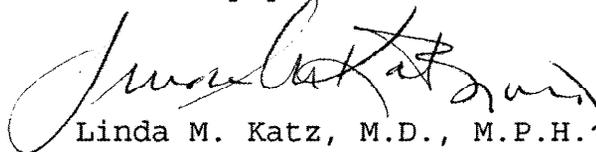
the size of the study, and the method of handling dropouts should be specified.

9. The protocol also does not assess the safety and effectiveness of these ingredients beyond 90 minutes. As it is possible that a toothache relief product could be used for several days to weeks, this issue needs to be addressed. Thus, a revised protocol to address the effectiveness and safety of benzocaine should be submitted.

10. In addition, the agency previously raised concerns about the risk of methemoglobinemia associated with benzocaine. Data from the sources outlined in your letter are acceptable to address this concern. Although the risk is low when benzocaine is used for relief of toothache pain, the product's labeling should warn of the remote possibility of methemoglobinemia occurring with topical application of benzocaine, especially in children.

Any comments you wish to provide should be submitted in triplicate, identified with the docket and comment numbers at the top of this letter, to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852. We hope this information will be helpful.

Sincerely yours,



Linda M. Katz, M.D., M.P.H.
Deputy Director
Division of OTC Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

REFERENCES

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE:

1-10-02

FROM:

Director
Division of OTC Drug Products, HFD-560

SUBJECT:

Material for Docket No. 81N-0033

TO:

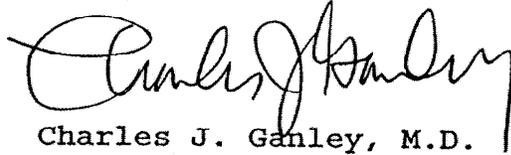
Dockets Management Branch, HFA-305



The attached material should be placed on public display under the above referenced Docket No.



This material should be cross-referenced to Comment No. PR5



Charles J. Ganley, M.D.

Attachment