

MEETING MINUTES

Docket #: 81N-0033
 Topic: Benzocaine for toothache relief
 Sponsor: Consumer Healthcare Products Association (CHPA)

Meeting Request Date: March 22, 2002
 Meeting Package Submission: April 16, 2002
 Meeting Date: June 3, 2002

Background

In the Oral Health Care proposed rulemaking, benzocaine is listed as Category III (meaning lack of data) to establish efficacy for the indication, relief of toothache pain. This meeting is the latest in a series of communications between CHPA and FDA regarding the effectiveness of benzocaine. FDA sent a letter dated January 8, 2002, which responded to CHPA's April 22, 1999, submission of a protocol evaluating the effectiveness of benzocaine and eugenol for the relief of toothache pain. CHPA requested this meeting to discuss issues raised by FDA in its January 8, 2002 letter. CHPA submitted a meeting package which included protocols for a pilot study of 20% benzocaine, clinical studies of 10% and 20% benzocaine, and a proposed consumer research study of reported usage patterns. Eugenol will be addressed separately at a later time.

Meeting AttendeesFDA Division of OTC Drug Products

Charles Ganley, M.D.	Division Director
Linda Katz, M.D., M.P.H.	Deputy Director
Debbie Lumpkins	Team Leader
Robert Sherman	IDS Reviewer
Elaine Abraham, R.Ph.	Project Manager
Rosemarie Neuner, M.D., M.P.H.	Medical Officer
David Hilfiker, M.S.	Chief, Project Management
Gerald Rachanow, P.D., J.D.	Regulatory Counsel

Division of Dermatology and Dental Drug Products

John Kelsey, D.D.S., M.B.A.	Dental Team Leader
Fred Hyman, D.D.S., M.P.H.	Dental Reviewer

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Division of Anesthetic, Critical Care, and Addiction Drug Products

Robert Rappaport, M.D.	Division Director
Nancy Chang, M.D.	Anesthesia Team Leader
Yaron Harel, M.D.	Medical Officer
Dionne Price, Ph.D.	Statistician

Consumer Healthcare Products Association

R. William Soller, Ph.D.	Senior Vice President, Director of Science and Technology
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CHPA Members and Other Participants

Barbara Cantor	Del Laboratories
William Cooley, Ph.D.	Cooley Consulting
Anthony DiMiceli, Ph.D.	Wyeth Consumer Healthcare
Elliot Hersh D.M.D., M.S., Ph.D.	University of Pennsylvania
Charles Hinkaty	Del Pharmaceuticals
Margaret Hughes, Ph.D.	Wyeth Consumer Healthcare
William Thompson, Ph.D.	Medical College of Georgia
Joel Waksman, Ph.D.	Wyeth Consumer Healthcare
Peter Walters	Del Pharmaceuticals
Lauren Schwartz	FDC Reports

Meeting Minutes

In opening remarks, Dr. Soller (CHPA) noted the difficulty in identifying the population of toothache sufferers, so the approach taken is not an actual use study.

The following questions were provided by CHPA and discussed:

- 1. Does the agency agree with an expanded definition of toothache, as defined by the entry criteria for the clinical efficacy studies?***

FDA does not have any objection to the sponsor's proposed study entry criteria, which defines toothache as tooth pain due to dental caries, loss of a restoration, or tooth fracture. FDA believes that the "open cavity" definition currently in the

proposed rulemaking covers the definition recommended by CHPA, but can clarify this in the final monograph.

2. ***Does the agency agree with the basic outlines (synopses) of the clinical studies for demonstrating the efficacy of 10% and 20% benzocaine for relief of toothache pain?***

FDA's comments on the proposed development plan are discussed below.

- a. ***In the clinical efficacy studies, will product application by the study subjects answer the agency's questions about directions for use relating to the amount of product self-applied at the site of perceived pain? Note: A pilot study is planned to help write the directions for use for the clinical efficacy studies, and product quantity will be measured.***

FDA questioned how the dose range of 225-375 mg of the product was derived, since many of the efficacy parameters are directly dependent on the magnitude and duration of analgesic relief produced by the product. Also, FDA asked for clarification on how consumers will measure 225-375 mg of product. CHPA stated that this dose range characterizes how these products have been used on the market. The directions for use include a schematic showing the amount of product to be placed on the user's finger for application. FDA responded that it is necessary to establish that consumers can measure accurately.

FDA pointed out that the submitted protocols will not provide information to support repeat dosing. Although there appears to be some attempt to measure the duration of effect, it is not clear how often a consumer will know when to re-apply the product. Therefore, data should be provided to support the product's dosing recommendations to consumers. FDA suggested that the pilot study be redesigned to be a multi-dose, "actual use" study, lasting 180-270 minutes, in which subjects self-apply the topical benzocaine according to the proposed product label. This would capture essential information regarding repeat dosing and the amount of product used.

FDA noted the importance of determining whether 20% benzocaine is better than 10%, and how the consumer would know which strength to use. Information is needed to support a dose response relationship between the 10% and 20% products. This can best be accomplished by studying each concentration within the same study. At least one of the studies should include a 10% and 20% treatment arm compared to placebo and establish a dose response.

FDA stated that it is unclear why the amount of product applied is listed as a primary efficacy parameter. CHPA explained that they want to ensure that the amount applied is not highly variable. They want to determine if the visual

display directing a consumer to the proper amount of product to apply will result in good compliance. FDA believes the primary efficacy parameter should reflect the direction for dosing four times daily. Data should be submitted supporting the compliance to the frequency of dosing listed in the proposed label. As the clinical study is designed to measure the efficacy of the products between 5 and 20 minutes, data are necessary to support a four times daily dosing regimen.

- b. For the clinical efficacy studies, does the agency agree with our responses to the agency's comments on the severity of pain at baseline, responder, definition of pain and pain relief scales, and definition of meaningful relief and onset and duration of effect, as detailed in the clinical synopses?***

FDA responded with the following information:

Severity of pain at baseline: CHPA's proposal to randomize patients with stratification by severity of pain at baseline is acceptable.

Definition of responder: A responder is a subject with a 1-unit improvement for 2 consecutive time points on both the pain relief and pain reduction scales, rather than the 2-unit improvement. This was requested in the FDA feedback letter dated January 8, 2002, and is acceptable. However, the results generated from the trials using a 1-unit improvement may preclude an indication for "relief of toothache." It may be more appropriate to characterize the use as "reduction in toothache pain."

Definition of pain and pain relief scales: The definitions for a 4-point dental pain scale and a 5-point dental pain relief scale are acceptable.

Definition of meaningful relief and onset and duration of effect: FDA finds the definitions acceptable but recommends the two-stopwatch method for the determination of onset of meaningful relief.

- 3. Does the agency agree with our consumer research approach to answer questions concerning frequency of product use and duration of product use?***

FDA had the following comments regarding this question:

Although the retrospective consumer usage survey may provide some interesting information, it will not provide sufficient information to support labeling regarding the frequency of repeat dosing and the amount of drug product used by the consumer. It is unlikely that a consumer will be able to provide accurate information on the use of a product that occurred up to 12 months prior to the survey. CHPA maintained that a consumer who has had toothache pain and used

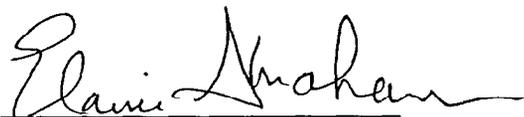
a benzocaine product would recall the pattern of use up to 12 months prior to the survey.

As neither the pilot study nor the proposed clinical efficacy studies are designed to assess consumer understanding or actual use of the product in an OTC setting, FDA suggested that a usage questionnaire could be included in packages of the marketed product. The questionnaire could be completed by consumers shortly after the time of use and submitted to the manufacturer.

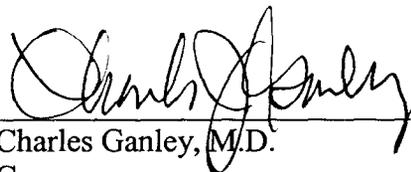
The clinical efficacy protocols can also include provisions to evaluate repeat dosing.

FDA had the following additional comments:

1. The basic fundamental use questions listed below should be addressed in order to label these products adequately.
 - Should a person who does not obtain relief with the initial dose use the product again?
 - Is there a limit on how much and how often the product should be used in a 24-hour period based on safety considerations?
2. The proposed labeling specifies not to use the product for more than 7 days. The need for using the product for 7 days should be explained. Any safety issues related to the use of benzocaine for this period of time should be addressed.
3. Information on how the risk of methemoglobinemia is going to be handled should be provided.



Elaine Abraham
Minutes Preparer



Charles Ganley, M.D.
Concurrence

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:

9/24/02

FROM:

Director
Division of OTC Drug Products, HFD-560

SUBJECT:

Material for Docket No. 81N-0033

TO:

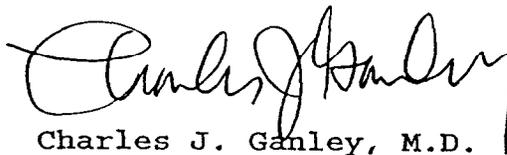
Dockets Management Branch, HFA-305



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



This material should be cross-referenced to Comment No. LET 56 & LET 51


Charles J. Ganley, M.D.

Attachment