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April 16, 2002

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
Food and Drug Administration
Rockville, MD 20857

RE: Docket No. 81N-003 Comment No. PR5

Dear Dr. Katz:

In preparation for the meeting that we requested in our letter of March 22, 2002, we submit this briefing document as background for our discussion. Our proposed program consists of four studies: Pilot Clinical Evaluation of 20% Benzocaine; Clinical Evaluation of 10% Benzocaine; Clinical Evaluation of 20% Benzocaine; and a Consumer Research Study on Reported Usage Patterns. We anticipate needing about one hour and a half for the meeting to discuss the rationale, objectives and design of the studies in the proposed program. This document is organized as follows:

- I. Questions to the Agency
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Should you require any clarification of this material or additional information that we might develop prior to our meeting, please feel free to contact Dr. Bill Soller at 202-429-3535, or his assistant, Mary McDonald, at 202-429-3531.

I. Questions to the Agency

We ask for discussion of the following questions/issues:

1. Does the agency agree with an expanded definition of toothache, as defined by the entry criteria for the clinical efficacy studies? (see Section II.A.1. and 2; see also Inclusion Criteria in clinical study synopses, Appendices B and C.)
2. Does the agency agree with the basic outlines (synopses) of the clinical studies for demonstrating the efficacy of 10% and 20% benzocaine for the relief of toothache pain? (See Appendices B and C for synopses)
 - a. In the clinical efficacy studies, will product application by the study subjects answer the agency's questions about directions for use relating to 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 (see Appendix A for synopsis of pilot study and Appendices B and C for clinical study synopses).
 - 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? (See Section III.C. and Appendices B and C for synopses)
2. Does the agency agree with our consumer research approach to answer questions concerning frequency of product use and duration of product use? (See sections II.B., III.A., III.C.6. and Appendix D.)

II. Background Information

A. Description of the OTC Condition, Definitions, and Intended Use

This section provides a description of the OTC condition, toothache, and definitions for agents for the relief of oral discomfort and agents for the relief of toothache.

1. Description of the OTC Condition, Toothache

For our purposes in developing evidence to support a toothache indication for benzocaine in the Final Monograph, toothache is defined as tooth pain most commonly results from decay, a lost restoration or a fractured tooth. When pulpal tissue is exposed directly or indirectly (via dentinal tubules) to pathogens and/or

environmental irritants such as hot or cold, the tooth pulp becomes hyperemic and pulpal nociceptors become activated leading to pain. In these situations, placing 10-20% benzocaine onto the affected tooth and/or around the immediate periodontal tissue may temporarily relieve the pain.

Specifically, the etiology of toothache that is self-treatable by benzocaine-containing OTC drug products is not just pain resulting from an open cavity in the tooth, but also pain resulting from loss of restoration or a fractured tooth. This definition should supersede the definition of toothache found in the Notice of Proposed Rulemaking (Tentative Final Monograph)¹. Our expanded definition is used as the basis for entry into the clinical efficacy studies, and we ask for the agency's concurrence on this.

On this point, a consumer would not likely be able to determine the exact cause of the toothache, despite appropriately self-selecting an OTC benzocaine-containing toothache remedy as a therapeutic bridge until professional care can be obtained.

2. Agents for the Relief of Oral Discomfort and for the Relief of Toothache

As defined in the Advance Notice of Proposed Rulemaking [FR 47 page 22716], an agent for the relief of oral discomfort is defined as “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.”

In the same document, an agent for the relief of toothache is defined as “an ingredient used for the temporary relief of pain arising as a result of an open tooth cavity.”² Per Section II.A.1. above, we propose amendment of this definition to “an ingredient used for the temporary relief of pain arising as a result of dental caries, loss of restoration, or fractured tooth.”

3. Intended Use of Toothache Products, As Defined by Market Research

OTC benzocaine-containing toothache products are intended to give temporary relief of toothache until the consumer can see a dentist for professional help. Long-term use of the product is not intended prior to a visit to a dentist. Market research information supports this type of limited self-use of OTC benzocaine-containing toothache remedies.

¹ “Therefore, the agency agrees with the Dental Panel that agents for the relief of toothache should be restricted to ingredients placed in a tooth cavity to relieve throbbing, persistent pain resulting from an open cavity in the tooth.” FROM: Advance Notice of Proposed Rulemaking on OTC Drug Products for the Relief of Oral Discomfort [47 Federal Register 22712-59 (5/25/82)]

² Advance Notice of Proposed Rulemaking on OTC Drug Products for the Relief of Oral Discomfort [47 Federal Register 22712-59 (5/25/82)]

For example, based on information from Simmons Market Research³ and Information Resources Inc., there are an estimated 7.3 million users of OTC benzocaine-containing products for toothache each year, with an estimated 9.8 million units of OTC benzocaine-containing products for toothache sold annually. Thus, on average 1.34 tubes of benzocaine are used per person annually by the population purchasing topical benzocaine-containing toothache remedies. It seems likely, therefore, that the very large majority of toothache users are applying such products for an acute episode of toothache.

B. Symptomatic Topical OTC Treatment of Toothache Is Infrequent: Implications for Subject Availability

Based on information from pre-study medication histories from past clinical trials submitted to the agency, and unit sales data, use of a topical treatment for relief of toothache is infrequent. This has an important bearing on whether a prospective actual use study is reasonably feasible in this OTC category (see sections II.B.3. and III. A.).

1. Pre-study Medication Histories

The table below taken from the 5 studies conducted by Del Pharmaceuticals and submitted to the agency in 1990 shows the number of patients reporting the use of medication taken for their toothache prior to entry into the study. In the one site located in the South (at the Medical College of Georgia in Augusta), 18 of 71 (25%) reported using a topical analgesic containing benzocaine. At the 4 other sites in the North, usage of Orajel or Anbesol ranged from 0% to 7%, with an average of 4%. For this table, all 367 subjects who were enrolled in the five studies were included in the tally regardless of treatment assignment or baseline pain.

Medication Taken for Toothache in Five Studies Conducted by Del Laboratories
Number of Responses

	Orajel	Anbesol	Tylenol	Aspirin	Other	None	Total
Med.Coll. GA	15	3	6	15	7	25	71
Rochcester	2	1	16	30	4	21	74
Tufts	1	3	5	15	9	40	72
Marquette	2	3	8	15	5	37	70
Essex	0	0	1	6	5	67	80
Total #	20	10	36	81	30	190	367
TOTAL %	5	3	10	22	8	52	

Note: There were no subjects who reported concomitant use of a benzocaine-containing OTC product and an oral analgesic prior to study entry.

³ Simmons Market Research uses a panel of approximately 30,000 adults, age 18+ as participants, each receiving one personal book and an additional household book which is completed by a designated member of the home. The book contains a detailed, multi-media section, demographics, personal information on product/service usage, lifestyle/ psychographic information and shopping behavior. This information was derived from Simmons Spring 2001 National Consumer Survey: Full Year/Weighted by Population.

In sum, less than 10% (30/367) of the subjects seen in dental clinics, which are the type of sites chosen for the proposed studies, reported using an OTC topical benzocaine product prior to presenting to the clinic. More subjects chose another form of pain relief, while the majority chose to “tough it out.”

2. Unit Sales Data Showing Low Annual Usage Per Person

The unit sales data and annual user-base data (see above) are consistent with the pre-study medication histories that show toothache to be a relatively infrequent condition with rather limited number of OTC usage episodes per person annually.

As restated from above, based on information from Simmons Market Research³ and Information Resources Inc., there are an estimated 7.3 million users of OTC benzocaine-containing products for toothache each year, with an estimated 9.8 million units of OTC benzocaine-containing products for toothache use sold annually. Thus, on average 1.34 tubes of benzocaine are used per person annually by the population purchasing topical benzocaine-containing toothache remedies.. [Note: as a point of reference, 476 million units of OTC internal analgesics, not including cough/cold use, are sold annually in the U.S.]

There are two conclusions to be drawn from this low average annual number of uses of topical benzocaine for toothache. First, it is likely that the large majority of toothache users are applying such products for an acute episode. However, this number is a mean, with an unspecified range. The proposed consumer research study that is linked to actual purchase data (see below re: consumer research proposal in Section III) will allow a determination of the exact dates of purchase and collection of consumer reports about reasons for purchase and use of the products, as well as other information (see synopsis in Appendix D).

Second, with such low usage, it would be extremely difficult to find sufficient numbers of individuals to undertake a prospective clinical trial on benzocaine effectiveness in an actual use setting. In this regard, it should be noted that the entry of persons in an emergency clinic of dental schools, as proposed in the clinical efficacy studies, is rather far along in the self-care paradigm of toothache treatment, and that benzocaine usage for an acute toothache episode at a time when they are expecting immediate professional care is a situation that perhaps represents a somewhat higher bar in terms of proving efficacy than in the early part of the self-care paradigm when the consumer is seeking a therapeutic bridge to professional care.

In sum, consumers who purchase OTC benzocaine-containing products for toothache typically use on average 1.34 tubes per year. This supports limited use of this type of product for an acute episode of dental pain, and suggests insurmountable hurdles to undertaking a prospective study.

3. Summary: Implications for Subject Availability and Types of Studies

Consumer data show that in comparison to OTC systemic analgesics, relatively few consumers with toothache choose to purchase an OTC benzocaine-containing product. The reasons for this may include the fact that for some the pain is tolerable without intervention, for others systemic analgesics are preferred, or there is a general lack of awareness of product availability. The greatest concentration of patients with toothache is found at dental school emergency clinics, and this is the most likely place to intercept consumers who used an OTC benzocaine-containing product. However, this is not the ideal setting for an actual-use clinical study since these patients have reached the end-stage of their self-treatment and have already made the decision to seek medical/dental intervention. It would be unreasonable and ethically questionable to expect that these patients would be willing to return home and restart a self-treatment cycle. Psychologically, one might expect a toothache sufferer to be willing to accept temporary relief or relief that takes the edge off the pain knowing that a professional appointment has been made within the next several days, versus an individual's willingness to endure pain for several days more having arrived at the emergency clinic for professional help.

Another possible approach would be to intercept the consumer at the point of purchase. However, this is logistically impractical because of the low purchase volume and widespread sales distribution. The largest volume retailer is Wal-Mart. On average, about two packages of the leading OTC topical benzocaine-containing products are sold per week per Wal-Mart store – for *all* uses, including toothache. Chains typically cannot or are not interested in recruiting subjects at the cash register for clinical trials, because of lack of scanner capabilities, unwillingness to slow the check-out line (particularly for a low volume product), unwillingness to train employees for clinical study selection, and/or unwillingness to challenge the retailer/customer relationship with an invasion of privacy. Indeed, the recent study by Ferris et al. (*Obstetrics and Gynecology* 99(3): 419-425, 2002) attempted such an approach for an OTC drug product, finding that the vast majority of individuals chose not to enter the trial (i.e., about 100 subjects in 2 years across 5 centers).

Hence, the most efficient approach is to identify consumers who recently purchased a benzocaine-containing product and conduct retrospective interviews on their demographics and usage patterns. This is possible by several methodologies commonly used by consumer research companies. As noted below, we believe that the approach most useful to address the agency's and our concerns is an approach that directly links actual purchasers to their recall of product use.

III. Overview, Rationale, and Comments Relating to the Proposed Program of Research

A. Overview and Rationale

Our proposed clinical program evaluates the efficacy of benzocaine 10% and 20% in two single-application, double-blind studies using subjects who are seeking treatment at

dental school emergency clinics. We have carefully considered this approach and believe it is the only feasible way to capture a sufficient sample and evaluate the target population with toothaches. However, for the reasons cited above, this is not a practical setting to assess actual-use or evaluate multiple-dose efficacy. In order to provide this information, we propose using a consumer research approach that identifies purchasers of benzocaine-containing products and then interviewing these consumers to assess how the product was used.

As shown in the previous section, usage of benzocaine-containing OTC toothache remedies is relatively low among persons presenting to a dental clinic.

We propose that our research program -- which includes a pilot study to define directions for use, the clinical studies on efficacy, and consumer research information from an existing panel of consumers tied to actual purchase pattern -- will adequately address the agency's questions pertaining to OTC use of benzocaine-containing toothache remedies. Taken together, this information should achieve the monograph requirement [21 CFR 330.1(a)(4)(ii)] of a "reasonable expectation of effectiveness."

B. Synopses of Proposed Studies: Clinical Efficacy Studies and Consumer Research

Appendices A – D provide synopses of the clinical protocols and consumer survey design for the proposed research program on benzocaine.

- A Pilot Clinical Evaluation of 20% Benzocaine
- B Clinical Evaluation of 10% Benzocaine
- C Clinical Evaluation of 20% Benzocaine
- D Consumer Research Study on Reported Usage Patterns

Pilot Study: In brief, the purpose of the pilot is to assess the methodology to be used in the larger prospective design clinical studies on the efficacy of 10% and 20% benzocaine for relief of toothache, to demonstrate that the label is adequate in terms of instructing the subjects to self-apply the product, and to demonstrate that the design is adequate to evoke usable data on efficacy in the use of benzocaine-containing OTC products for treatment of toothache. The pilot will assess 20 patients in terms of their self-application of approximately 300 mg of gel product, equivalent to 60 mg benzocaine, applied by the subjects consistent with label directions. See synopsis for further details (Appendix A).

Clinical Efficacy Studies: The hypothesis for the double-blind, randomized (stratified by baseline pain), single-dose, placebo-controlled, parallel, multi-center clinical study on 20% benzocaine in 200 patients suffering from spontaneous toothache due to dental caries, loss of a restoration or tooth fracture is: 20% benzocaine is significantly more effective than placebo for relief of toothache pain. An identical study is proposed for 10% benzocaine vs. placebo. Subjects will be assessed for their ability to self-apply, consistent with label directions, approximately 300 mg of gel product (equivalent to 60 mg for 20% benzocaine; 30 mg for 10% benzocaine), and for their responses to the test

product or placebo. See synopses for further details (Appendices B and C). We go into less detail about these studies and the agency's prior concerns in this section, as we address them below in detail in Section III.C.

Consumer Research Study: The agency has asked for an assessment of consumer usage patterns for benzocaine-containing products for toothache. The impracticalities of undertaking a prospective actual use study (see above) appear insurmountable; hence, we propose using an established consumer panel of 65,000 households with complete purchase data to identify consumers who report having purchased OTC benzocaine-containing products for toothache. This panel was created five years ago by Information Resources Inc. and is the basis for the regularly reported, government-sponsored Consumer Confidence Index. The uniqueness of this panel is that all products purchased by the head of the household, who is the panel representative, are scanned by the UPC code. These data are downloaded automatically on a weekly basis into a central database. Hence, there is the opportunity to link actual purchase behavior with reported usage behavior.

The purpose of the consumer research study is to assess the reported usage patterns of known purchasers of OTC benzocaine-containing products to determine products and reported use patterns during acute toothache episodes. Study parameters will include among other parameters (see study synopsis): name of product(s) purchased; reason for use; type and strength of product; number of products purchased in last 12 months; number of times product was applied for the acute episode; number of tube(s)/bottle(s) of product(s) used for the acute episode; interval(s) between applications; overall effectiveness; adverse experiences; whether professional help was sought to resolve the toothache; reported professional diagnosis of cause of the toothache; whether the toothache recurred; whether the panelist has dental coverage; and use of other products concomitantly with benzocaine products for relief of toothache during the same acute episode.

Study parameters confirmed by Information Resources Inc.'s sales linkage database include: confirmation of that a benzocaine product was purchased by respondent in last 12 months; number of products purchased in last 12 months; time between purchases in last 12 months; actual date(s) of purchase(s); actual product(s) purchased, including brandname and concentration (10% or 20%); size(s) (SKUs) purchased; demographic information about purchaser and respondent; location of purchase; confirmation of concomitant product use for relief of toothache during the same acute episode.

C. Specific Comments Relating to the Proposed Clinical Program

1. Directions for Use: Self-Application and Amount of Product Self-Applied

FDA Comment⁴: "Information showing that consumers understand how to use benzocaine for toothache relief in an OTC setting should be provided."

⁴ See Attachment E for letter from FDA to CHPA dated January 8, 2002.

FDA Comment: "...assess the amount of product necessary to achieve the desired effect..."

CHPA Response: The pilot study will be used to write the directions for use which will be used by the subjects in the clinical studies to self-apply the product. The pilot study and clinical studies will assess (by weight) the amount of product self-applied as well as the pain intensity baseline and pain intensity and global relief.

2. Definition of Responder

FDA Comment: "'responder' should be defined as a subject who achieves a 2-point improvement on the pain relief scale."

FDA Comment: "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."

CHPA Response: In the clinical efficacy studies on 10% and 20% benzocaine, a responder is defined as "a subject who experiences pain improvement, as exhibited by a pain-score reduction on the DPS from baseline of at least 1 unit, at any 2 consecutive time points between 5 and 20 minutes." For a subject with severe pain, a 1-unit reduction in pain represents 33% of the range of the pain scale since the range of improvement for these subjects is 3 units in length. For a subject with moderate initial pain, a 1-unit reduction on the pain scale represents a 50% reduction of the range of the pain scale, since for these patients the range of improvement is 2 units in length. Thus, we agree with the agency that a 1-point difference in the dental pain scale may be different for subjects with differing baseline pain; however, the ordinal properties of the scale hold, and in either case the subject is indicating a substantial amount of pain improvement.

In order for a subject with moderate pain to satisfy a 2-point reduction criterion, a *complete* alleviation of the pain in a relatively short amount of time would be necessary. This is an unreasonably strict demand on an OTC treatment, especially one that is intended to be a bridge to treatment of the toothache by an appropriate health care professional.

3. Definition of Meaningful Pain Relief and Onset and Duration of Effect

FDA Comment: "Meaningful relief (secondary effectiveness parameter) and duration of relief should be defined."

CHPA Response: Subjects will press a stopwatch when they experience relief which, in their opinion, is "meaningful." Onset of Meaningful Relief will be defined as the elapsed time from dosing displayed on the stopwatch, and it must be

confirmed by the pain severity at the immediately following assessment being less than the baseline pain by at least 1 unit.

Duration of effect (rather than relief) will be defined as the time difference between onset of effect and its offset. Onset of effect is the first timepoint at which two consecutive pain scores that are less severe than at baseline by at least 1 unit are attained. Offset of effect is the first timepoint following onset of effect at which two consecutive pain scores that are no less severe than at baseline are attained.

4. Initial Pain of Moderate Severity

FDA Comment: “only individuals with severe pain be included so that the study can show a significant improvement with benzocaine compared to placebo.”

CHPA Response: The task group understands the agency’s concern, but believes the studies can be appropriately powered to permit baseline pain of moderate and severe intensity.

In order to gain a greater understanding of how different measures of effectiveness can affect the interpretation of the efficacy of benzocaine in reducing toothache pain, the percentages of responders in the previously conducted Del and Wyeth Consumer Healthcare (WCH, formerly Whitehall Robins Healthcare) studies⁵ were reanalyzed. To keep the comparisons between the two companies’ studies simple, only the 20% and placebo cases were used in the Del studies since the WCH studies were executed with only their 20% benzocaine product compared to a placebo. These analyses were compromised by the use of a 5% benzocaine “pretreatment” in all groups, a flaw already acknowledged by the agency. However, they are data available for examining the role of different measuring parameters of efficacy. Individuals were considered responders if they experienced a rapid lessening of their pain, as measured on a 4-point scale (None, Mild, Moderate, or Severe) administered at various time points. Specifically, a reduction in pain from the pre-treatment level by at least a specified amount for at least two consecutive time points within the first 20 minutes in the WCH studies or within the first 25 minutes in the Del studies (since those studies did not have a 20-minute pain assessment) was required. Two consecutive time points were required for confirmation purposes. The pain descriptors in the WCH studies were None, Slight, Moderate, Severe and Very Severe. In the analyses below, the subjects with Very Severe pain were deleted, and subjects rating their pain as “slight” were treated as those in the Del studies as “mild.”

These analyses were performed to help answer the following questions:

⁵ Note: the subjects from the two sites (MCG and Essex) that were excluded from the agency’s analysis described in FDA’s first feedback letter to CHPA were not included in this analysis.

- Does benzocaine's effectiveness for severe toothaches differ from its effectiveness for moderate ones?
- How does the percentage of responders depend on the required amount of pain reduction? Three thresholds were considered: a) at least a 2-point reduction, b) at least a 1-point reduction, c) pain reduced to no worse than mild levels.

The results, including the percentage of responders in the benzocaine and placebo groups, as well as the p-value from an analysis testing whether these percentages were significantly different from one another, are tabulated below. The key findings, which are consistent across the Del and WCH studies, are as follows:

Benzocaine was more effective among individuals entering with moderately painful toothaches than among those entering with severe toothaches, regardless of the required amount of pain reduction. The reason for this is unclear, but perhaps individuals with severe toothaches have suffered nerve damage, thus affecting their sensation of pain and pain relief.

Benzocaine's effectiveness, relative to placebo, was most evident when a 1-point reduction in pain was required and least evident when a 2-point reduction was required, especially among subjects with moderate pre-treatment pain. A 1-point reduction from baseline represents 33% of the range of the 4-point pain scale and is thus indicative of meaningful effect. In order for an individual with moderate pain to satisfy the 2-point reduction criterion, a *complete* alleviation of the pain in a relatively short amount of time would be necessary. This is an unreasonably strict demand on an OTC treatment, especially one which is intended to be a bridge to treatment of the toothache by an appropriate health care professional.

**Percent of Responders for Two Consecutive Time Points
within 20 (WCH studies) or 25 (Del studies) Minutes**

Del Studies				
Subjects	Treatment	Reduction\geq2	Reduction\geq1	Pain\leqMild
All	Benz 20%(n=70)	44	77	57
	Placebo (n=70)	21	36	21
	p-value	.003	.001	.001
Moderate	Benz 20% (n=25)	40	76	76
	Placebo (n=21)	14	14	14
	p-value	.060	.001	.001
Severe	Benz 20% (n=43)	49	79	49
	Placebo (n=49)	25	45	25
	p-value	.019	.001	.019

Note: two subjects in the Del studies who had mild baseline pain were excluded from the subgroup analysis by severity. P-values are from the CMH test controlling for center.

WCH Studies

Subjects	Treatment	Reduction \geq 2	Reduction \geq 1	Pain \leq Mild
All	Benz 20%(n=85)	26	62	39
	Placebo (n=86)	35	51	34
	p-value	.199	.142	.483
Moderate	Benz 20%(n=25)	20	72	72
	Placebo (n=20)	25	35	35
	p-value	.683	.016	.016
Severe	Benz 20%(n=48)	25	56	25
	Placebo (n=52)	35	56	35
	p-value	.248	.947	.248

Note: 26 subjects in the WCH studies who had very severe baseline pain were excluded from the subgroup analysis by severity. P-values are from the CMH test controlling for center.

Combined Studies

Subjects	Treatment p-value	Reduction \geq 2	Reduction \geq 1	Pain \leq Mild
All	p-value	.320	.001	.001
Moderate	p-value	.265	.001	.001
Severe	p-value	.448	.025	.448

Note: two subjects in the Del studies who had mild baseline pain; 26 subjects in the WCH studies who had very severe baseline pain were excluded from the subgroup analysis by severity. P-values are from the CMH test controlling for center.

Taken together, these findings indicate that a new study to assess benzocaine’s efficacy in toothache pain should include subjects with either moderate or severe pain. Since a 1-point reduction in pain is meaningful, and demanding at least a 2-point reduction is unreasonable especially when the pain is of moderate severity to begin with, the criterion used in the definition of a responder should incorporate a 1-point reduction.

4. Statistical Test Methods and Power Calculations

FDA Comment: ... “the statistical test methods, power calculations to determine the size of the study, and the method of handling dropouts should be specified.”

CHPA Response: These will be described in the final protocol. Drop-outs are discussed in the last section of each synopsis (see Appendices B and C).

5. Use Pattern and Multiple Use

FDA Comment: “the safety and effectiveness of these ingredients beyond 90 minutes”

CHPA Response: An open-label in-home actual use study is unrealistic (see sections II.B.3. and III.B.). Toothache pain consistent with the label indication is a relatively rare and unpredictable phenomenon, as noted above; hence a prospective design is not realistic. Sending subjects with dental pain home for professional treatment the following day, once they have presented to an emergency dental clinic, is not likely to receive favorable IRB approval, nor help recruitment.

6. Methemoglobinemia

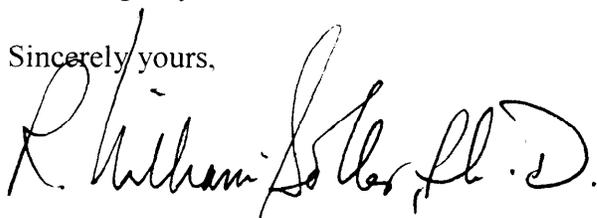
FDA Comment: “risk of methemoglobinemia...”

CHPA Response: The issue of methemoglobinemia is not directly addressed in these protocols, except as the provision for documenting treatment-related adverse experiences is concerned. This subject will be addressed separately.

IV. Summary

In conclusion, CHPA has attempted to find effective ways to answer the questions posed by the agency in its January 8, 2002, letter. Using a combined clinical and consumer research approach, we believe that we will be able to overcome the substantial difficulties in prospectively identifying consumers with toothache pain prior to presentation to an emergency dental clinic. Given that the monograph definition of effectiveness, which is the basis for general recognition of effectiveness [21 CFR 330.1(a)(4)(ii)], is a “reasonable expectation of effectiveness,” we believe our proposed research program is responsive to the agency’s concerns, and we look forward to our upcoming discussion on this matter.

Sincerely yours,



R. William Soller, Ph.D.
Senior Vice President and
Director of Science and Technology

- Appendices:
- A Pilot Clinical Evaluation of 20% Benzocaine: Study Synopsis
 - B Clinical Evaluation of 10% Benzocaine: Study Synopsis
 - C Clinical Evaluation of 20% Benzocaine: Study Synopsis
 - D Consumer Research on Usage Patterns: Study Synopsis
 - E FDA Letter to CHPA Dated January 8, 2002

APPENDIX A**PILOT CLINICAL EVALUATION OF 20% BENZOCAINE
STUDY SYNOPSIS**

TITLE:	Pilot Clinical Evaluation of the Efficacy of 20% Benzocaine for the Relief of Toothache
STUDY NUMBER:	TBD
PRINCIPAL INVESTIGATOR:	TBD
STUDY OBJECTIVE:	<p>To assess the methodology to be used in the larger prospective design clinical studies on the efficacy of 10% and 20% benzocaine for relief of toothache</p> <ul style="list-style-type: none">• Demonstration that the label is adequate in terms of instructing the subjects to use the product• Demonstration that the design is adequate to evoke usable data on efficacy and to collect retrospective information on the use of benzocaine-containing OTC products for treatment of toothache
STUDY DESIGN:	Single dose, open-label, single center
ESTIMATED DURATION OF STUDY:	1 month
DURATION OF EVALUATION:	90 minutes
NUMBER OF SUBJECTS:	20
DOSAGE:	Application of approximately 300 mg of gel product (placebo or for active, equivalent to 60 mg benzocaine), consistent with label directions, applied by the subjects
INCLUSION CRITERIA:	<ol style="list-style-type: none">a. Presence of spontaneous toothache due to dental caries, loss of a restoration, or tooth fracture.b. Presence of moderate or severe baseline

pain, defined as a score of 2 (moderate) or 3 (severe) on a 0 to 3 scale on the Dental Pain Scale.

- c. Subjects must be reliable, cooperative, and of adequate intelligence to read and understand the rating scale and other study instructions.
- d. Subjects must be able to read, comprehend, and sign the consent form.

EXCLUSION CRITERIA:

- a. History of sensitivity or allergy to benzocaine or other local anesthetic agents.
- b. Use of any systemic or topical analgesic or herbal product within 2 hours of enrollment.
- c. Use of a sustained-release or long-acting Rx or OTC analgesic product (i.e., sustained-release Tylenol® or Aleve®) within 6 hours of enrollment.
- d. Use of any centrally acting CNS depressants, including first-generation antihistamines, within 8 hours of enrollment.
- e. Ingestion of alcohol-containing products within 6 hours of enrollment.
- f. Presence of a periodontal abscess.
- g. Presence of concomitant oral pain due to soft-tissue (e.g., aphthous or traumatic ulcer, herpes labialis, ANUG) lesions or multiple hard-tissue (e.g., carious) lesions.
- h. Previous participation in the study.
- i. Member or a relative of the study site staff or sponsor directly involved in the study.
- j. Use of an investigational drug within the past 30 days.

STUDY PARAMETERS

Baseline:

Dental Pain Scale: How much pain do you have now? (4-point categorical scale: 0=None, 1=Mild, 2=Moderate, 3=Severe)

Products and patterns of product use during the acute toothache episode prior to entry into the clinic.

STUDY PARAMETERS continued... Post-Baseline:

- Dental Pain Scale (5-30 min: 5-minute intervals; 30-90 minutes: 10-minute intervals)
- Stopwatch: Onset of Meaningful Relief
- Dental Pain Relief Scale: (none, a little, some, a lot, complete); (5-30 min: 5-minute intervals; 30-90 minutes: 10-minute intervals)
- Adverse Experiences: These will be recorded as they occur.

EFFICACY ANALYSIS:

Primary Efficacy Parameter

- Amount of product applied. Note: at least 90% of the subjects should apply an amount of product that is in the range of 225-375 mg of gel.
- Percentage of responders, where a responder is a subject who experiences pain improvement, as exhibited by a pain-score reduction on the DPS from baseline of at least 1 unit, at any 2 consecutive time points between 5 and 20 minutes.

Secondary Efficacy Parameter

- Time to onset of meaningful relief among *all* subjects
- Duration of effect among *all* subjects (as assessed by the dental pain scale)
- SPRID at 30 minutes

Other Parameters

- Time to onset of effect among just the responders in the benzocaine 20% group
- Duration of effect
- Descriptive analysis of the products and patterns of product use prior to and during the acute toothache episode of the study

DROPOUTS

Responder Status: Subjects dropping out will be considered non-responders unless they have already met the criteria to be considered responders.

Onset of Meaningful Relief: Subjects dropping out before attaining onset will be considered censored for analysis purposes. The censoring will be at the end of the scheduled evaluation (90 minutes) if the dropout is due to lack of efficacy (LOE), otherwise it will be at the time of the dropout.

Duration of Effect:

- Before onset of effect: Duration will be considered 0 minutes if the dropout is due to LOE; otherwise the subject will be excluded from this analysis.
- After onset of effect: Duration will be calculated as the dropout time minus the onset time if the dropout is due to LOE; otherwise, the subject will be considered censored for this analysis with a censoring time equal to the dropout time minus the onset time.

APPENDIX B**CLINICAL EVALUATION OF 10% BENZOCAINE
STUDY SYNOPSIS**

TITLE: Clinical Evaluation of the Efficacy of 10% Benzocaine for the Relief of Toothache

STUDY NUMBER: TBD

PRINCIPAL INVESTIGATOR: TBD

STUDY OBJECTIVE: To evaluate the clinical efficacy of 10% benzocaine for relief of toothache

HYPOTHESIS: 10% benzocaine is significantly more effective than placebo for toothache pain

STUDY DESIGN: Double-blind, randomized (stratified by baseline pain), single-dose, placebo-controlled, parallel, multi-center

ESTIMATED DURATION OF STUDY: 18 months

DURATION OF EVALUATION: 90 minutes

NUMBER OF SUBJECTS: 200 (100 per group)

SAMPLE SIZE DETERMINATION: A sample size of 100 subjects per treatment group will provide approximately 80% power to detect significant differences, assuming that the response rates are 50% in the benzocaine group and 30% in the placebo group.

DOSAGE: Application of approximately 300 mg of gel product (placebo or for active, equivalent to 30 mg benzocaine), consistent with label directions, applied by the subjects

INCLUSION CRITERIA:

- a. Presence of spontaneous toothache due to dental caries, loss of a restoration, or tooth fracture.
- b. Presence of moderate or severe baseline pain, defined as a score of 2 (moderate) or 3 (severe) on a 0 to 3 scale on the Dental Pain Scale.
- c. Subjects must be reliable, cooperative, and of adequate intelligence to read and understand the rating scale and other study instructions.
- d. Subjects must be able to read, comprehend, and sign the consent form.

EXCLUSION CRITERIA:

- a. History of sensitivity or allergy to benzocaine or other local anesthetic agents.
- b. Use of any systemic or topical analgesic or herbal product within 2 hours of enrollment.
- c. Use of a sustained release or long-acting Rx or OTC analgesic product (i.e., sustained-release Tylenol® or Aleve®) within 6 hours of enrollment.
- d. Use of any centrally acting CNS depressants, including first-generation antihistamines, within 8 hours of enrollment.
- e. Ingestion of alcohol-containing products within 6 hours of enrollment.
- f. Presence of a periodontal abscess.
- g. Presence of concomitant oral pain due to soft-tissue (e.g., aphthous or traumatic ulcer, herpes labialis, ANUG) lesions or multiple hard-tissue (e.g., carious) lesions.
- h. Previous participation in the study.
- i. Member or a relative of the study site staff or sponsor directly involved in the study.
- j. Use of an investigational drug within the past 30 days.

STUDY PARAMETERS

Baseline:

Dental Pain Scale: How much pain do you have now? (4-point categorical scale: 0=None, 1=Mild, 2=Moderate, 3=Severe)

STUDY PARAMETERS continued

Products and patterns of product use during the acute toothache episode prior to entry into the clinic

Post-Baseline:

- Dental Pain Scale (5-30 min: 5-minute intervals; 30-90 minutes: 10-minute intervals)
- Stopwatch: Onset of Meaningful Relief
- Dental Pain Relief Scale: (none, a little, some, a lot, complete); (5-30 min: 5-minute intervals; 30-90 minutes: 10-minute intervals)
- Adverse Experiences: These will be recorded as they occur.

EFFICACY ANALYSIS:

Primary Efficacy Parameter

- Percentage of responders, where a responder is a subject who experiences pain improvement, as exhibited by a pain-score reduction on the DPS from baseline of at least 1 unit, at any 2 consecutive time points between 5 and 20 minutes.

Secondary Efficacy Parameter

- Time to onset of meaningful relief among *all* subjects
- Duration of effect among *all* subjects (as assessed by the dental pain scale)
- SPRID at 30 minutes

Other Parameters

- Time to onset of effect among just the responders in the benzocaine 10% group
- Duration of effect among just the responders in the benzocaine 10% group
- Descriptive analysis of the products and patterns of product use prior to entry and during the acute toothache episode of the study

DROPOUTS

Responder Status: Subjects dropping out will be considered non-responders unless they have already met the criteria to be considered responders.

Onset of Meaningful Relief: Subjects dropping out before attaining onset will be considered censored for analysis purposes. The censoring will be at the end of the scheduled evaluation (90 minutes) if the dropout is due to lack of efficacy (LOE), otherwise it will be at the time of the dropout.

Duration of Effect:

- Before onset of effect: Duration will be considered 0 minutes if the dropout is due to LOE; otherwise the subject will be excluded from this analysis.
- After onset of effect: Duration will be calculated as the dropout time minus the onset time if the dropout is due to LOE; otherwise, the subject will be considered censored for this analysis with a censoring time equal to the dropout time minus the onset time.

APPENDIX C**CLINICAL EVALUATION OF 20% BENZOCAINE
STUDY SYNOPSIS**

TITLE:	Clinical Evaluation of the Efficacy of 20% Benzocaine for the Relief of Toothache
STUDY NUMBER:	TBD
PRINCIPAL INVESTIGATOR:	TBD
STUDY OBJECTIVE:	To evaluate the clinical efficacy of 20% benzocaine for relief of toothache
HYPOTHESIS:	20% benzocaine is significantly more effective than placebo for toothache pain
STUDY DESIGN:	Double-blind, randomized (stratified by baseline pain), single-dose, placebo-controlled, parallel, multi-center
ESTIMATED DURATION OF STUDY:	18 months
DURATION OF EVALUATION:	90 minutes
NUMBER OF SUBJECTS:	200 (100 per group)
SAMPLE SIZE DETERMINATION:	A sample size of 100 subjects per treatment group will provide approximately 80% power to detect significant differences, assuming that the response rates are 50% in the benzocaine group and 30% in the placebo group.
DOSAGE:	Application of approximately 300 mg of gel product (placebo or for active, equivalent to 60 mg benzocaine), consistent with label directions, applied by subjects.

INCLUSION CRITERIA:

- a. Presence of spontaneous toothache due to dental caries, loss of a restoration, or tooth fracture.
- b. Presence of moderate or severe baseline pain, defined as a score of 2 (moderate) or 3 (severe) on a 0 to 3 scale on the Dental Pain Scale.
- c. Subjects must be reliable, cooperative, and of adequate intelligence to read and understand the rating scale and other study instructions.
- d. Subjects must be able to read, comprehend, and sign the consent form.

EXCLUSION CRITERIA:

- a. History of sensitivity or allergy to benzocaine or other local anesthetic agents.
- b. Use of any systemic or topical analgesic or herbal product within 2 hours of enrollment.
- c. Use of a sustained release or long-acting Rx or OTC analgesic product (i.e., sustained-release Tylenol® or Aleve®) within 6 hours of enrollment.
- d. Use of any centrally acting CNS depressants, including first-generation antihistamines, within 8 hours of enrollment.
- e. Ingestion of alcohol-containing products within 6 hours of enrollment.
- f. Presence of a periodontal abscess.
- g. Presence of concomitant oral pain due to soft-tissue (e.g., aphthous or traumatic ulcer, herpes labialis, ANUG) lesions or multiple hard-tissue (e.g., carious) lesions.
- h. Previous participation in the study.
- i. Member or a relative of the study site staff or sponsor directly involved in the study.
- j. Use of an investigational drug within the past 30 days.

STUDY PARAMETERS

Baseline:

Dental Pain Scale: How much pain do you have now? (4-point categorical scale: 0=None, 1=Mild, 2=Moderate, 3=Severe)

STUDY PARAMETERS continued

Products and patterns of product use during the acute toothache episode prior to entry into the clinic.

Post-Baseline:

- Dental Pain Scale (5-30 min: 5-minute intervals; 30-90 minutes: 10-minute intervals)
- Stopwatch: Onset of Meaningful Relief
- Dental Pain Relief Scale: (none, a little, some, a lot, complete); (5-30 min: 5-minute intervals; 30-90 minutes: 10-minute intervals)
- Adverse Experiences: These will be recorded as they occur.

EFFICACY ANALYSIS:

Primary Efficacy Parameter

- Percentage of responders, where a responder is a subject who experiences pain improvement, as exhibited by a pain-score reduction on the DPS from baseline of at least 1 unit, at any 2 consecutive time points between 5 and 20 minutes.

Secondary Efficacy Parameter

- Time to onset of meaningful relief among *all* subjects
- Duration of effect among *all* subjects (as assessed by the dental pain scale)
- SPRID at 30 minutes

Other Parameters

- Time to onset of effect among just the responders in the benzocaine 20% group
- Duration of effect among just the responders in the benzocaine 20% group
- Descriptive analysis of the types and patterns of product use prior to and during the acute toothache episode of the study

DROPOUTS

Responder Status: Subjects dropping out will be considered non-responders unless they have already met the criteria to be considered responders.

Onset of Meaningful Relief: Subjects dropping out before attaining onset will be considered censored for analysis purposes. The censoring will be at the end of the scheduled evaluation (90 minutes) if the dropout is due to lack of efficacy (LOE), otherwise it will be at the time of the dropout.

Duration of Effect:

- Before onset of effect: Duration will be considered 0 minutes if the dropout is due to LOE; otherwise the subject will be excluded from this analysis.
- After onset of effect: Duration will be calculated as the dropout time minus the onset time if the dropout is due to LOE; otherwise, the subject will be considered censored for this analysis with a censoring time equal to the dropout time minus the onset time.

APPENDIX D**CONSUMER RESEARCH ON REPORTED USAGE PATTERNS
STUDY SYNOPSIS**

TITLE:	Consumer research study on reported usage patterns of OTC benzocaine-containing products for toothache
PRINCIPAL INVESTIGATOR:	IRI
STUDY OBJECTIVE:	To assess the reported usage patterns among consumers who have actually purchased an OTC benzocaine-containing product for relief of toothache
STUDY DESIGN:	A retrospective open label reported usage study using an established research panel used for the Consumer Confidence Index
ESTIMATED DURATION OF STUDY:	6 months
NUMBER OF SUBJECTS:	At least 300 completed subjects from IRI's established 65,000-member household panel, screened for product usage in the last 12 months

NOTE: toothache as a condition is likely to be remembered by subjects

Estimated recruitment calculations:

- 65% response rate to mail questionnaire (IRI) (42,250 of 65,000 household panel)
- 5-8% usage rate per household for all indications (AC Nielsen) (2,112-3,380 of 42,500)
- 30% of product usage in benzocaine category used for toothache (633-1,014 of 2,112 – use in last 12 months)
- Subset of users (use in last 6 months): (316-507)

INCLUSION CRITERIA:	<p>Purchase of a benzocaine-containing product as confirmed by the IRI database</p> <p>Reported use of benzocaine-containing product for toothache</p> <p>NOTE: Subjects will be identified by IRI's standard mail soliciting procedure (bimonthly), with panelists' responses by mail</p>
EXCLUSION CRITERIA:	<p>NOTE: We are only contacting only consumers we know purchased the product, so there is no exclusion.</p>
STUDY PARAMETERS	<p><u>Screening Using IRI's Standard Bimonthly Mailer:</u> Report of purchase of benzocaine-containing product for toothache</p> <p><u>Reported Usage Survey:</u> Products and reported use patterns during the acute toothache episodes, including:</p> <ul style="list-style-type: none">▪ Name of product(s) purchased▪ Reason for use▪ Type and strength of product▪ Number of products purchased in last 12 months▪ Number of times product was applied for the acute episode▪ Number of tubes of product used for the acute episode▪ How the product was applied (Q-tip or finger)▪ Interval between applications▪ Overall effectiveness▪ Any adverse experiences▪ Whether professional help was sought to resolve the toothache▪ Reported professional diagnosis of cause of the toothache▪ Whether the toothache recurred▪ Whether the panelist has dental coverage▪ Use of other products concomitantly with benzocaine products for relief of toothache

during the same acute episode

STUDY PARAMETERS continued

Study Parameters Confirmed by IRI's Sales Linkage Database

- Confirmation of that a benzocaine product was purchased by respondent in last 12 months
- Number of products purchased in last 12 months
- Time between purchases in last 12 months
- Actual date of purchase
- Actual product purchased, including brand name and concentration (10% or 20%)
- Size (SKU) purchased
- Demographic information about purchaser and respondent
- Location of purchase
- Confirmation of concomitant product use for relief of toothache during the same acute episode

ASSESSMENTS:

- Descriptive cross tabulations based on study parameters
- Subset assessments, among others, of consumers reporting:
 - Single product use for the acute episode by strength, frequency, type of application, effectiveness: in last 6 months; in last 12 months
 - Multiple product use or frequent and/or sequential benzocaine product use for the same acute episode by strength, frequency, type of application, effectiveness: in last 6 months, in last 12 months
 - Benzocaine use for toothache, which was not diagnosed as toothache resulting from dental caries, fractured tooth, or loss of restoration: in last 6 months; last 12 months
 - Adverse experiences
 - Overall effectiveness



JAN 8 2002

Food and Drug Administration
Rockville MD 20857

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

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

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cc: HFA-305(Docket No. 81N-0033/PR5)
HFD-560:Ganley/Katz/Lumpkins/Sherman/Keravich
HFD-540:Kelsey/Hyman
R/D:RSherman/11/05/01
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