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Center for Drug Evaluation and Research
Food and Drug Administration
DHHS/FDA/CDER/OND
10903 New Hampshire Ave WO22
Silver Spring, MD 20903

Re: Docket No. 1981N-0033; Comment Number C76

Dear Dr. Ganley:

Reference is made to your feedback letter of February 24, 2006, and the December 20, 2004 submission that included a draft protocol, BZ-03-07, "Benzocaine Gel Toothache Dose-Response Study." This study is intended to support the classification of benzocaine as generally recognized as safe and effective for the temporary relief of toothache pain in the Final Monograph for OTC Oral Health Care Drug Products.

The Consumer Healthcare Products Association Oral Discomfort Task Group (the Task Group)[1] appreciates the comments of FDA in the February 24, 2006, feedback letter and understands that these comments are FDA's best advice on designing a protocol to address the safety and efficacy of benzocaine for the relief of toothache pain. As you recommended, we have included a revised final protocol for your final review. Areas that have been changed are highlighted.

Upon review of your comments, the Task Group identified four areas of comment where we either disagree with the recommendation or for which we are providing additional data. These are FDA comments: #1, #2, #3, and #5.

FDA Comment #1
"Analyses of the Dental Pain Scale (DPS) data have been proposed as your primary efficacy endpoint. While DPS is recognized as a validated metric, we recommend that you consider the use of a visual analog scale (VAS) score for pain assessment

[1] The Consumer Healthcare Products Association Oral Discomfort Task Group consists of those OTC manufacturing companies who manufacture and distribute OTC benzocaine-containing products for the temporary relief of toothache pain. The Task Group members are Wyeth Consumer Healthcare and Del Laboratories.

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throughout the trial (in addition to the proposed baseline assessment). VAS has been more widely validated and may provide a more precise measure, particularly of the onset and duration of pain relief. If both DPS and VAS metrics are employed, you should identify a priori, the specific analyses of each metric that will serve as primary and secondary endpoints."

The Task Group proposes to utilize only the four-point categorical DPS as described in the current protocol as the primary efficacy endpoint measure, since we believe that this is a well-recognized, highly sensitive, and validated methodology that is appropriate for the proposed study.

The four-point DPS has been used in pain studies for decades and has been found to be both reliable and sensitive. The Guidelines for the Clinical Evaluation of Analgesic Drugs, published in 1979 and updated in 1992, clearly indicate that the categorical pain intensity and relief scales are sensitive and validated methods. A review of analgesic Summary Bases for Approval, published in 2004, further indicated that such methods were commonly applied in clinical trials of analgesic drugs[2]. Therefore, this four-point categorical DPS, as defined in this protocol, is appropriate for the measurement of benzocaine efficacy for the relief of toothache pain. The pilot benzocaine efficacy study (BZ-03-08), which was previously submitted to the Agency for review, as well as three studies submitted by Del Laboratories, Inc., utilized the DPS methodology. The outcomes of these studies indicate that the DPS agrees and correlates well with the subject's own assessment of pain intensity in this spontaneous toothache model.

In order to capture the onset and offset of pain relief, the current study design involves 15 pain assessments within the 2-hour study period that are 5 and 10 minutes apart. At each of these time points, the subject is required to provide two assessments: their pain intensity and pain relief relative to baseline pain. We do not believe that the addition of another metric, the VAS, would provide additional value. We are also concerned that adding the VAS measurement could be confusing to subjects with so little time between assessments.

We do plan to use VAS, as defined in the protocol, at study entry only to verify that each subject had at least moderate baseline pain in order to qualify for inclusion into the study.

FDA Comment #2
"A clinically and statistically significant difference between active and placebo treatments will be required of the primary endpoint to support efficacy, for each strength. The magnitude of a clinically significant difference between active and

[2] Ridgway, D. Analgesics for acute pain: Meeting the United States Food and Drug Administration's requirements for proof of efficacy. Clin J Pain 2004: 20 123-132.

placebo treatments must be defined in the protocol and the definition must be supported by data. . . ."

The Task Group believes that a 10-percentage point difference in the number of responders observed between the placebo and benzocaine (in all subjects or only among those subjects suffering from severe toothache pain) is sufficient to define a clinically meaningful difference in response. As FDA requested, the magnitude of a clinically significant difference between active and placebo treatments has been defined in protocol section 8.3.1 (Primary Efficacy Parameters) and data have been provided.

We have conducted a review of clinical studies that defined a clinical and statistical significance based on evaluation of the percentage of responders. These examples were used to support drug approval. Examples of drugs for which approvals were based on approximately a 10-percentage point difference in response rate between active and placebo treatments (data from Summary Bases of Approval) include:

- 2% Amlexanox (aphthous ulcers)
- Zelnorm® (irritable bowel syndrome)

Drug/Product	% Responders (Active Treatment)	% Responders (Placebo)	Percentage Point Difference in Responders
2% Amlexanox (OraDisc™)	30.4	21.9	8.1
Zelnorm®			
Study 1	39	28	11
Study 2	44	39	5
Study 3	43	38	5

Benzocaine products, which are marketed at 10% and 20% strengths, are intended to provide "temporary relief of discomfort," as stated in the proposed amendment to the tentative final monograph for OTC oral health care drug products to include products for relief of oral discomfort.[3] Thus, the data shown in the table above indicate that a 10-percentage point difference in the outcome between active and placebo is within the efficacy range of approved drugs and is appropriate for use in this study.

FDA Comment #3
"As proposed, a difference of 5 percent in the number of responders between the 10 and 20 percent strength benzocaine active treatment groups on the DPS would be

[3] Fed. Reg. 56 (185): 48302-47, September 1991.

considered clinically significant, whether it occurs across the entire population or only within the subgroup of patients presenting with severe toothache at baseline. The definition of a clinically significant difference (e.g., the proposed 5 percent difference) should be supported by data."

The Task Group believes that a response rate for the higher dose that is 5 percentage points higher than the lower dose is clinically meaningful. We selected the proportion of people who achieved a self-assessed one-unit change in pain intensity based on a 4-point categorical scale (DPS) as a responder and based our outcome measure on a responder analysis. This is defined in protocol section 8.7 (Establishment of a Dose-Response Relationship).

The pilot benzocaine study (BZ-03-08) showed a close temporal correlation between a one-unit decrease in pain intensity and the self-report of meaningful relief. The response represents a meaningful change in pain perception to the individual and is therefore clinically meaningful to that individual.

The clinical significance of a 5-percentage point difference in responders between two doses of a drug is also supported by the magnitude of the outcome difference between regular and extra strength acetaminophen. A recent Cochrane systematic review[4] revealed that the number needed to treat (NNT) for 50% maximum TOTPAR in single-dose, placebo-controlled postoperative pain trials was 4.6 for acetaminophen 600/650 mg and 3.8 for acetaminophen 975/1000 mg. Recalling that NNT is the reciprocal of the proportion of subjects achieving the response threshold, the relative benefit of extra strength over regular strength can be derived:

$$(1/3.8) - (1/4.6) = 0.0457$$

Thus, in this meta-analysis, there is a 5-percentage point difference in the number of subjects reaching the response threshold when comparing extra strength and regular strength acetaminophen. Thus, a 5-point difference has been accepted as being a clinically significant difference.

FDA Comment #5
"A two-stopwatch technique for determining onset of meaningful relief should be used, as discussed at the June 3, 2002, meeting."

The Task Group believes that the single-stopwatch method, as proposed in this protocol, is reliable and better suited for this study than the two-stopwatch technique. We

[4] Barden J, Edwards J, Moore A, McQuay H. Single-dose oral paracetamol (acetaminophen) for postoperative pain (Review). The Cochrane Database of Systematic Reviews 2004 (1) Art No. CD004602. DOI: 10.1002/4651858.CD004602.

acknowledge that the two-stopwatch method has been widely used to distinguish the onset of meaningful relief from the first perception of relief in the evaluation of systemic analgesic drugs in post-surgical or acute pain studies. The single-stopwatch method is, however, also widely accepted and has been used successfully as a meaningful method to capture the fact that a patient obtained meaningful pain relief and the time it occurred. The single-stopwatch technique is also better suited for this protocol for the following reasons:

- In the proposed protocol, the onset of meaningful relief as measured by the stopwatch timing is not considered as the primary efficacy endpoint and is not intended for use as the primary criterion for advertising claims on efficacy. This measurement is only intended as a secondary endpoint to corroborate the onset of relief as assessed by subjects in response to the dental pain and dental pain relief scales.
- We believe that the addition of a second stopwatch could be too complicated to the subjects in this study design. Topically applied benzocaine, a fast-acting topical anesthetic, is expected to have a fast onset. Unlike in the acute pain studies with systemic analgesic drugs where the pain assessments are made at longer time intervals (every 15 to 30 minutes), subjects in the proposed topical benzocaine for toothache pain protocol are required to make pain and pain relief evaluations every 5 minutes during the first 30 minutes to ensure that the onset of clinically meaningful pain relief is correctly captured.

* * * * * * * * * *

For the remainder of the FDA comments, the Task Group agrees with the FDA perspective and has incorporated these comments into the accompanying final protocol. The following lists the FDA comments and our proposed action steps.

FDA Comment #2 (continued)
". . . We recommend that for trials of pain medication, the assessment of onset, duration, and magnitude of pain relief be compared to the outcome of a global satisfaction assessment as a means of demonstrating clinically significant difference between treatments."

The Task Group agrees with FDA's recommendation to add a global satisfaction assessment and has modified the final protocol (sections 3.0, 6.1, 6.2.3, 6.3.5, and 8.3.2, and the corresponding sections in the Synopsis) to reflect the inclusion of the Global Satisfaction Assessment as follows:

> At the end of the 120-minute evaluation period or when a subject requests rescue medication, the subject will be asked the following question for a global assessment of the study medication:
>
> "How would you rate this medication for temporary relief of toothache pain?" The assessments will be based on the following scale: poor = 0, fair = 1, good = 2, very good = 3, excellent = 4.

This assessment will be considered as a secondary efficacy endpoint.

FDA Comment #4
"A secondary endpoint would be expected to show a trend supporting the primary endpoint outcome for us to make a determination of efficacy for each of the active treatments compared to placebo. Likewise, the existence of a dose response relationship between active treatment strengths would need to be supported with similar findings between the primary and secondary endpoints."

The Task Group agrees with the Agency that the majority of the secondary endpoints should be supportive of the primary measure of efficacy.

FDA Comment #6
"Instructions for uniform selection and dosing of rescue medications should be included in the protocol for both pediatric and adult subjects."

The Task Group agrees with this FDA recommendation and has revised protocol section 6.6 (Rescue Medication) as follows:

> <u>Proposed revision:</u>
> "All subjects including 12-18 year olds who do not experience pain relief or whose pain returns any time before the 120-minute time point will be allowed to ingest the rescue analgesic ibuprofen 200-400 mg or acetaminophen 1000 mg (for those who are aspirin or NSAID intolerant) according to label directions."

FDA Comment #7
"Pain relief combined with pain intensity difference score (PRID) was not clearly defined. Verification should be provided to indicate that it is the 'pain relief intensity difference,' calculated by adding the Pain Intensity Differences (PID) and Dental Pain Relief Scale (DPRS) scores at each post-dosing point."

Protocol section 8.4.2. (Derived Endpoints) and the corresponding section in the protocol synopsis have been revised to verify how the pain-relief intensity difference is calculated. The revised protocol reads as follows:

Proposed revision:
"Pain relief scores combined with pain intensity difference scores (PRID) will be calculated by adding the Pain Intensity Differences (PID) and Dental Pain Relief Scale (DPRS) at each post-dosing time point."

FDA Comment #8
"The means of weighing the sum of pain relief combined with pain intensity difference (SPRID) scores by time was not specified."

The protocol section 8.4.2. (Derived Endpoints) and the corresponding section in the protocol synopsis have been revised to specify the means of weighing the sum of pain relief combined with pain intensity difference scores by time.

Proposed revision:
"SPRID: time-weighted (weighted by time since the prior scheduled assessment) sum of PRID scores, over 60 and 120 minutes."

FDA Comment #9
"Regarding secondary efficacy parameter #3 (SPRID scores over 30, 60, 90, 120 minutes) and parameter #4 (pain relief combined with PRID at each measurement time): by including the four testing periods for parameter #3 (30, 60, 90 and 120 minutes) and 15 testing periods for parameter #4, there are total of 22 separate comparisons for secondary endpoints. This raises the problem of multiple comparisons and needs correction or reduction of the number of variables."

We point out that these parameters are secondary comparisons to support the primary efficacy variable and are not intended for additional claims. Nevertheless, to address the concerns regarding multiplicity, the Task Group accepts FDA's suggestion to reduce the number of variables. The Task Group proposes to restrict statistical analysis of SPRID to the 1st and 2nd hour for SPRID, eliminating the 30- and 90-minute summaries.

FDA Comment #10
"The protocol should be written to specify who should measure the dose, particularly for children (age 12 and under)."

The Task Group has revised protocol sections 6.1.m and 6.1.n. (Study Conditions) to specify that the subject should measure and apply the dose.

Proposed revision:
m. "All subjects including 12-18 year olds will be given a card that contains the label directions and a picture of how much gel they should apply to the painful tooth and surrounding gum tissue."

n. "All subjects including 12-18 year olds will be asked to self-apply an amount of the study gel, consistent with the picture on the label directions card, to the affected tooth and surrounding gum tissue. Subjects will be allowed to look in a mirror to correctly locate the affected tooth, if needed."

FDA Comment #11
"Subjects with glucose-6-phosphate dehydrogenase (G6PD) deficiency and severe respiratory problems that are likely to be adversely affected by methemoglobinemia should be excluded from the trials."

The Task Group has revised section 4.3 and the study synopsis (Exclusion Criteria) to exclude subjects reporting glucose-6-phosphate dehydrogenase (G6PD) deficiency or a history of acute or chronic hemolytic anemia.

However, the Task Group has not identified any specific respiratory problem that warrants exclusion from the study. In reviewing the Adverse Experience Reporting System (AERS) and Spontaneous Reporting System (SRS) databases and the literature on methemoglobinemia, Dr. Elliot Hersh, Associate Dean of Clinical Research at the University of Pennsylvania, found no instances of methemoglobinemia associated with OTC benzocaine use among those with severe respiratory problems. During the last 10 years, more than 100 million units of benzocaine-containing oral care products have been sold. In light of this extensive exposure, we did not see any signal in the spontaneous adverse event reporting databases to warrant exclusion of consumers with any particular respiratory disease in this study.

FDA Comment #12
"Subject safety should be proactively assessed at regular intervals during the 2-hour observation period. These evaluations should include vital sign measurements, as well as assessments of level of wakefulness and symptoms associated with local anesthetic toxicity such as light headedness, paresthesias, and nausea. The protocol should provide a plan for management of patients who appears to be experiencing distress."

To proactively assess the safety of subjects during the 2-hour observation period, section 6.4 (Safety Assessment) of the protocol has been revised to include the following safety assessments:

"Vital signs including blood pressure, pulse rate and respiratory rate will be measured at 0, 1 and 2 hours post-dosing."

> "Subjects will be asked the non-leading question, "How do you feel?" at 1 and 2 hours post-dosing, to assess symptoms associated with potential local anesthetic toxicity such as lightheadedness, paresthesias, and nausea."

Section 7.0 (Safety) of the protocol has been revised to include the following plan for management of patients who appear to be experiencing distress:

> "The Investigator must provide documentation for the study file to affirm that their research clinic is prepared for handling anesthetic medical emergencies. The clinic must have access to emergency equipment and staff trained in managing anesthetic medical emergencies."

At the Agency's recommendation to submit the final protocol for review 30 days prior to initiating the study, the Task Group requests rapid review and agreement to the final protocol that is submitted with this letter.

If you have any questions, please contact me at 202-429-3533.

On behalf of the CHPA Oral Discomfort Task Group,

Sincerely,

Lorna C. Totman

Lorna C. Totman, Ph.D., DABT
Acting Vice President
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Attachment: Protocol BZ-03-07

cc: Division of Dockets Management (HFA-305)
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