



*Producers of Quality
Nonprescription Medicines and
Dietary Supplements for Self-Care*

CONSUMER HEALTHCARE PRODUCTS ASSOCIATION®

June 21, 2002

Charles Ganley, M.D.
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. Ganley:

Thank you for the helpful input on the Oral Discomfort Task Group's proposed research program on benzocaine for toothache. This follow-up letter covers three basic areas: a review of the points discussed and agreed upon at the feedback meeting of June 3rd; our response to the number and type of studies required to establish benzocaine's efficacy for toothache; and some suggested next steps. This letter does not address the issues regarding repeat dosing of benzocaine. We realize the importance of the labeling regarding repeat dosing, and we are currently considering various approaches to address this difficult and pivotal issue. We hope to send you our proposal within the next few weeks.

We understand from the discussion that the Agency agrees on the following points:

- Definition of toothache as described in our background document for the feedback meeting;
- Definition of responder, the pain relief scales, and duration of effect, as detailed in the clinical efficacy study synopses;
- Definition of onset of meaningful relief, as detailed in the clinical efficacy study synopses with the modification that a double-stopwatch method will be used for confirmation;
- Subjects will be required to have either moderate or severe toothache pain in order to enter the efficacy studies;
- Self application of the product by study subjects as being suitable to assess drug efficacy in the clinical trial;
- A single clinical trial to establish efficacy of benzocaine for toothache may be sufficient depending on the support provided by the previously conducted Del studies.

In addition, during the meeting the Agency indicated that finalization of the oral pain monograph is not currently scheduled.

We propose to confirm the efficacy of the product and address the labeling issue regarding amount of product to apply in the following two studies:

1. A pilot study to demonstrate that study subjects with toothache understand the eventual proposed directions of use. Directions based on the results of this study will be used in

81N-0033

LET 53

the clinical efficacy study;

2. One double-blind, single-dose, placebo-controlled clinical efficacy study with 20% benzocaine to define clinical efficacy for toothache after subject application of the product;

This list of activities includes a single study to confirm efficacy and does not include a dose-response study. We believe that the clinical information that is already available substantiates the effectiveness of benzocaine and supports a dose-response relationship between the 10% and 20% strengths of benzocaine. This latter information is detailed in an attachment prepared by William O. Thompson, Ph.D. (Professor and Director Emeritus of Biostatistics, Medical College of Georgia). Dr. Thompson concludes:

"The analyses presented in this paper specifically examine the data using current statistical methodology for testing dose-response relationships using categorical data analysis techniques. The data establish a strong presumption of both the efficacy and the dose response of benzocaine."

Finally, we suggest the following next steps:

1. Review of the enclosed document by the FDA team addressing benzocaine in the context of the need for a dose-response study and/or more than one study.
2. CHPA will submit to the Agency within the next few weeks our proposal to address the issues related to repeat dosing.

We look forward to your early response. If a conference call with our group would be helpful to clarify points raised in this correspondence, we would welcome that discussion.

Sincerely yours,



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

Attachment: William O. Thompson, Ph.D.(Professor and Director Emeritus of Biostatistics, Medical College of Georgia):Analysis of Orajel Efficacy Using Three Studies Approved by the FDA's Feedback Letter of 1998

ATTACHMENT**Analysis of Orajel Efficacy Using Three Studies
Approved by the FDA's Feedback Letter of 1998
June 10, 2002**

William O. Thompson, Ph.D.
Professor and Director Emeritus of Biostatistics
Medical College of Georgia

Prepared for the CHPA Oral Discomfort Task Group

Introduction

This report provides a retrospective analysis of the efficacy of benzocaine as an agent in the relief of toothache pain, using a new definition of a "responder" approved by the Food and Drug Administration (the agency) and announced in a meeting on June 3, 2002. The data are from three clinical studies previously submitted to the agency by Commerce Drug Company (now Del Pharmaceuticals, Inc.) in 1991. These studies have been previously analyzed by Del and independently by the agency using other definitions of a responder. The agency's findings were published in the feedback letter dated July 20, 1998 as part of Docket 81N-0033. The studies were selected by the agency from five studies conducted from 1981 to 1986 and submitted to the agency in 1991 as evidence of the efficacy of benzocaine as a toothache remedy.

In the June 3 meeting the agency also expressed interest and concern regarding a dose response of benzocaine as an agent for the temporary relief of toothache pain. The analyses presented in this paper specifically examine the data using current statistical methodology for testing dose-response relationships using categorical data analysis techniques. The data establish a strong presumption of both the efficacy and the dose response of benzocaine.

Description of the Studies

The study protocols have been described in detail in previous submissions and captured in the agency's feedback letter. Patients arriving at emergency clinics at dental schools were given an opportunity to enroll in a 95-minute study designed to test the efficacy of benzocaine as a temporary toothache remedy. Treatments were randomized; they included a placebo, a gel containing 10% benzocaine, and a gel containing 20% benzocaine. To further protect the study blind, a gel containing 5% benzocaine was used under the tongue prior to application of the study medication to the affected tooth. Patients were asked to report their pain on a 4-level Likert scale using the pain descriptors "none," "mild," "moderate" or "severe." Patients were further asked to report their pain after 5 minutes of application and every 10 minutes thereafter, until either their pain had returned to baseline or 95 minutes had elapsed. Once a patient's pain returned to baseline, that patient was removed from the study, and treatment was scheduled.

Patients were to be enrolled in the study if their baseline pain was moderate or severe. Patients were randomized to a treatment group irrespective of the status of their baseline pain. No effort was made to balance or otherwise control for baseline pain as a condition for patient enrollment. Two patients who enrolled with mild pain at the Marquette site were excluded from these analyses and those by the agency in 1998.

Methods and Procedures

At the meeting on June 3 the agency was interested in data supporting a dose response in the efficacy of benzocaine for temporary relief of toothache. The three submitted studies were randomized trials conducted with similar protocols, and all studies contained three treatment groups, a placebo, and two doses (10% and 20%) of benzocaine. Thus the data from these studies are appropriate for evaluating a dose response.

The statistical methods used in the analyses are standard methods for categorical analyses. The methods are explained, with examples and references, including SAS code, in chapters 4 and 5 of *Categorical Data Analysis Using the SAS System* by Stokes, ME; Davis, CS; and Koch, GG; and published by the SAS Institute Inc., Cary, NC, 1995. Overall dose response is tested with a Mantel-Haenszel (MH) statistic, having a single degree of freedom that tests the trend in the response in the three ordered levels of benzocaine concentration. (This test is comparable to the Cochran-Armitage trend test.) Data were analyzed by site and across sites. The analysis across sites was tested using the Cochran-Mantel-Haenszel (CMH) statistic for "Row mean scores differ." For simplicity in the tables, both the MH and CMH statistics are labeled CMH, as they are under the standard format from SAS output.

As additional reference information, p-values of Fisher's Exact test are shown for testing the significance of the efficacy difference between only the 10% and 20% benzocaine groups. Significance levels (p-values) are shown for both the two-sided test and the correct one-sided test, reflecting the significance of an increase in the efficacy rate from the 10% to the 20% group. Fisher's Exact tests were conducted rather than Chi-square tests because in some cases the expected number of patients in some of the tabulated cells was too small for valid Chi-square tests. The Fisher's Exact test provides a test for a one-sided alternative hypothesis, which is appropriate to the hypothesis under study (since a decrease in response rate from 10% to 20% benzocaine is of no interest).

Analyses are given for the proportion of patients experiencing pain relief (responders) using two definitions of a responder:

- A patient experiencing pain reduction of at least one level at two consecutive times within 20 minutes. This is the definition accepted by the agency at the June 3 meeting. Applying this definition to this study, a responder must have reported pain at least one level lower than baseline at both the 5-minute and 15-minute times.
- A patient experiencing any pain relief (a definition used by the agency in the feedback letter). This definition was operationalized in the current data set by declaring any patient a responder who reported a pain measure lower than baseline at any time before leaving the study.

Results

The Study Sample

Table 1 gives the sample size, by study location, of the data presented in this report.

Table 1. Number of Patient Records by Study Location

No. of Patients	Study Location
72	Tufts University, School of Dental Medicine, Boston, MA
68	Marquette Univ., School of Dentistry, Milwaukee, WI
74	Univ. of Rochester, School of Medicine and Dentistry, Rochester, NY
214	Total Number of Patients

Study Site and Baseline Pain

Table 2 shows the distribution of patients by study site and baseline pain. Since moderate or severe baseline pain was not a criterion for entry to the study, differences in baseline pain at the sites reflect differences in patient pools at the sites.

Table 2. Distribution of Patients by Site and Baseline Pain

<u>Initial Pain</u>	<u>Marquette</u>	<u>Rochester</u>	<u>Tufts</u>	<u>Total</u>
Moderate	46	14	10	70
Severe	22	60	62	144
Total	68	74	72	214

There were more patients with moderate pain at the Marquette site than at the other two sites. Thus results of analyses by study site may reflect potential differences in how patients with moderate or severe baseline pain respond to benzocaine. There were twice as many patients with severe baseline pain in the analysis, so sub-analyses by baseline pain will be more powerful in the severe group than in the moderate group.

Analysis of Efficacy

Analyses of efficacy were conducted using the two definitions of a responder given above. Table 3 shows the percent of responders, by site and concentration of benzocaine, the p-value of the CMH statistic that tests the correlation of percent effective across the increasing concentration levels of benzocaine, and the p-values of the one-sided and two-sided Fisher's Exact test of the significance of the difference between the 10 and 20 percent concentrations of benzocaine.

**Table 3. Percent Responders by Site and Concentration of Benzocaine
(Responder: A Patient with Pain Relief at Both 5 and 15 minutes)**

Concentration of Benzocaine	Site			
	Marquette (n = 68)	Rochester (n = 74)	Tufts (n = 72)	All sites (n = 214)
0	18.2	34.6	40.9	31.4
10	64.0	54.2	59.3	59.2
20	61.9	75.0	78.3	72.1
CMH p-value	.0041	.0045	.0112	0.0001
<u>Tests on the benzocaine groups:</u>				
Fisher's exact p-value (two-sided)	1.0000	0.2270	0.2252	0.1176
Fisher's exact p-value (one-sided)	0.6751	0.1135	0.1287	0.0744

The CMH trend statistic testing the dose response of benzocaine was significant at each site and across sites. This significance is driven in part by the efficacy of either strength of benzocaine as compared to a placebo. When the three sites are combined to gain statistical power, a directional test of significance for increased response at the 20% level of benzocaine over the 10% level applied only to these two groups nearly reaches traditional statistical significance ($p = 0.0744$).

The similarity of percent responders for the 10% and 20% benzocaine groups at Marquette likely reflects the large number of patients at that site with moderate baseline pain. When the same data were analyzed by baseline pain across the sites (Table 4), the results showed an overall dose-response relationship for each level of baseline pain. In the moderate baseline pain group, the mean numbers of responders to both the 10% and 20% benzocaine group were similar, while there was an almost 20-percentage-point increase in the mean percent of responders from the 10% to the 20% benzocaine groups in the patients with severe baseline pain.

No analyses were conducted in which both baseline pain and study site were simultaneously studied, because the number of patients in each group was small, owing to the uneven distribution of moderate cases in the database.

**Table 4. Percent Responders by Baseline Pain and Concentration of Benzocaine
(Responder: A Patient with Pain Relief at Both 5 and 15 minutes)**

Concentration of Benzocaine	Baseline Pain	
	Moderate (n = 70)	Severe (n = 144)
0	14.3	38.8
10	62.5	57.7
20	64.0	76.7
CMH p-value	.0012	.0003
<u>Tests on the benzocaine groups:</u>		
Fisher's exact p-value (two-sided)	1.0000	0.0803
Fisher's exact p-value (one-sided)	0.5740	0.0403

The CMH trend statistic testing the dose response in each group of patients is driven in part by the effectiveness of benzocaine over placebo. The increased effectiveness of 20% benzocaine over 10% benzocaine, when testing only the two benzocaine groups, is seen in the group of patients with severe baseline pain ($p = 0.0403$) but not in the moderate baseline pain ($p = 0.5740$) group.

Analyses of efficacy were also conducted using the agency's definition of responder: a patient with any pain relief. Although the agency prepared its database from the patient records independently, a comparison of numbers in the table on page 6 of the feedback letter and the totals (not shown) in Table 6 of this report shows differences of only one or two patients in any group. Thus the data sets appear comparable.

The data presented in Table 5 parallel the data presented in Table 3, and the data in Table 6 parallel the data presented in Table 4.

**Table 5. Percent Responders by Site and Concentration of Benzocaine
(Responder: A Patient with Pain Relief at Any Time)**

Concentration of Benzocaine	Site			
	Marquette (n = 68)	Rochester (n = 74)	Tufts (n = 72)	All sites (n = 214)
0	36.4	57.7	40.9	45.7
10	80.0	83.3	63.0	75.0
20	90.5	95.8	91.3	92.7
CMH p-value	.0001	.0011	.0004	0.0001
<u>Tests on the benzocaine groups:</u>				
Fisher's exact p-value (two-sided)	0.4285	0.3475	0.0238	0.0064
Fisher's exact p-value (one-sided)	0.2869	0.1738	0.0202	0.0038

**Table 6. Percent Responders by Baseline Pain and Concentration of Benzocaine
(Responder: A Patient with Pain Relief at Any Time)**

Concentration of Benzocaine	Baseline Pain	
	Moderate (n = 70)	Severe (n = 144)
0	38.1	49.0
10	87.5	69.2
20	100.0	88.4
CMH p-value	.0001	.0001
<u>Tests on the benzocaine groups:</u>		
Fisher's exact p-value (two-sided)	0.1099	0.0217
Fisher's exact p-value (one-sided)	0.1099	0.0281

Results from these analyses are similar to those using the new definition of a responder.

Discussion

The results from these analyses are supportive of benzocaine as an agent for temporary relief of toothache. The following generalizations are supported by the data presented:

- The data establish a strong presumption of both the efficacy and the dose response of benzocaine.
- There was an almost 20-percentage-point increase in the efficacy of benzocaine in the group of patients reporting severe baseline pain. This increase was noted using both the new definition of responder approved by the agency and the "responder at any time" definition used by the agency in 1998.

The significance of the dose response of benzocaine, clearly establishing efficacy, was seen in every site among patients with differing blends of moderate and severe baseline pain. The studies in each site were relatively small, limited to no more than 25 patients per treatment group. Statistical significance of a dose response consistently found in small studies supports a true and clinically meaningful effectiveness of the drug.

The findings of this analysis support a heterogeneous dose response among the patients with moderate versus severe baseline pain. The percentage of responders with moderate pain was similar for the two concentrations of benzocaine, while the percentage of responders with severe pain was increased for the higher concentration of benzocaine. There were half as many patients enrolled with moderate pain as with severe pain, so the power to detect differences in efficacy is lower for moderate pain. However, a heterogeneous dose response is clinically intuitive for the toothache indication and supports the continued use of two concentrations of benzocaine on the market.