

ATTACHMENT III

## Attachment III

### CHPA Benzocaine Task Group Perspective on Questions

1. **Does the Agency agree with the proposed OTC labels (Del Pharmaceuticals and Wyeth Consumer Healthcare) for benzocaine-containing products marketed for toothache?**
  - a. **Does the Agency agree that the direction for the amount of product to use is sufficiently clear that consumers will apply the appropriate dose of the product?**
  - b. **Does the Agency agree that benzocaine may be used up to 4 times daily but not more often than every 2 hours, or as directed by a dentist or physician?**

Appendix I contains proposed monograph labeling for benzocaine-containing products for the temporary treatment of toothache pain. Please note that labeling for the Wyeth Consumer Healthcare product is for both the temporary relief of pain associated with toothache and temporary relief of pain associated with canker sores, dentures, braces, sore gums, and minor dental procedures.

- a. Does the Agency agree that the direction for the amount to use is sufficiently clear that consumer will apply the appropriate dose of the product?

We are proposing use of a pictogram to show consumers how much product they should apply to the painful tooth and surrounding gum tissue. We propose that the Directions section of Drug Facts contain a mound-shaped diagram of product which is 1.0 cm at the base by 0.8 cm at the height. This pictogram is intended to guide consumers to dispense the appropriate amount of product on the fingertip to apply to the affected tooth and surrounding gum tissue. This amount corresponds to about 200-400 mg of product or 40-80 mg of benzocaine from 20% benzocaine-containing formulation.

Data from clinical study BZ-03-08 support that this direction for use is effective in conveying to consumers the amount of product to apply to the affected area. In the clinical study, 30 subjects were presented with the label and asked to self-apply product to the fingertip. The amount of product dispensed was determined by weighing the product tube before and after dispensing the product. The median amount of product dispensed from the tube was 327 mg. There was a range of 88.1 mg to 1646.7 mg., with the next highest value being 658 mg. Thus, the median amount of benzocaine dispensed was 66 mg (if all subjects had received the active treatment). Importantly, greater than 85% of subjects placed less than 400 mg of product or 80 mg of benzocaine on their fingertip. (See Table B.2 in Appendix II).

We therefore believe these data support the use of a pictogram to aid the consumer in deciding how much product to use.

b. Does the Agency agree that benzocaine may be used up to 4 times daily but not more often than every 2 hours, or as directed by a dentist or physician?

In the 29 October 2002 FDA feedback letter, the Agency indicated that the “time of subsequent doses in labeling can be based on evaluation of the duration of effect data obtained from the proposed clinical efficacy study.” In the clinical study (BZ-03-08), we measured the duration of effect as defined as the time difference between onset of effect and its offset. The median duration of relief for the benzocaine group was >115 minutes (the observation period ended at 2 hours) (See Table B.5. in Appendix II). In addition, more than half of the subjects in the benzocaine treatment group remained in the study during the full 120 minute time period without re-medicating (See Table B.8. in Appendix II). Based on these data, we propose that the labeling for benzocaine-containing products for the temporary treatment of toothache contain directions that the product may be used up to 4 times daily, but not more often than every 2 hours.

**2. Based on our review of the updated safety assessment of reports and literature reports of methemoglobinemia associated with the use of benzocaine-containing products for toothache, we conclude methemoglobinemia is an extremely rare event. Therefore, does the Agency agree that a specific methemoglobinemia warning statement is not necessary?**

A review of the FDA Adverse Experience Reporting System (AERS) and Spontaneous Reporting System (SRS) databases from January 1969 through the second quarter of 2003 showed only 6 alleged cases of methemoglobinemia associated with OTC oral care benzocaine-containing products over the 34.5 year period (Appendix III). During the last 10 years, more than 100 million units of benzocaine-containing oral care products were sold indicating that the number of cases of methemoglobinemia associated with the use of oral care products is exceedingly rare.

The FDA also asked for an updated assessment of reports of methemoglobinemia associated with the use of benzocaine products for the temporary relief of toothache pain. Wyeth Consumer Healthcare and Del Pharmaceuticals, Inc. reviewed adverse event reports received over the past 7 years. Neither company received any reports of methemoglobinemia associated with the use of oral care benzocaine products for the relief of toothache pain.

In a review of the relevant literature on methemoglobinemia (Appendix IV), Dr. Elliot Hersh, Associate Dean of Clinical Research at the University of Pennsylvania, found only three cases of methemoglobinemia associated with the use of oral care products in children greater 2 years of age, or in adults. The two cases in children were either a result of accidental ingestion or application of excessive amounts of

product by a maxillofacial/oral surgeon. The adult case involved use of an entire bottle of Anbesol. All of these cases involved acute overdoses of benzocaine-containing oral products. Dr. Hersh concludes that, based on his review of the literature, it is extremely unlikely that the current labeling of 20% benzocaine-containing products could result in clinically significant methemoglobinemia.

Based on our review of the AERS and SRS databases, adverse events reported to Wyeth Consumer Healthcare and Del Pharmaceuticals, and Dr. Hersh's review of the clinical literature, we conclude that methemoglobinemia associated with the use of oral care products is exceedingly rare and, therefore, no specific methemoglobinemia warning statement is necessary on benzocaine-containing products for toothache.

**3. Does the Agency agree that the results from clinical study BZ-03-08, in conjunction with results of previous Del clinical results which evaluated the efficacy of both 10% and 20% benzocaine, are sufficient to establish monograph status for toothache, and therefore no additional clinical study is necessary?**

We propose that the results from the CHPA Benzocaine Task Group (BTG) clinical study BZ-03-08, together with those from the previously conducted Del studies, sufficiently prove the effectiveness of benzocaine for toothache pain. The Del studies, which showed benzocaine 10% and 20% to be effective, were criticized by the Agency as having some operational shortcomings. The BTG clinical study corrected the shortcomings in the Del methodology, and it resulted in similar findings. This indicates that the results of the Del studies were valid. The following table lists the results for key efficacy variables that could be measured in both sets of studies.

	Studies	Placebo	Benz 10%	Benz 20%	p-value <sup>1</sup>
<b>Proportion (%) responders (primary efficacy parameter)</b>	<b>Del</b>	22/70 (31.4)	46/76 (60.5)	50/68 (73.5)	<0.001 <sup>2</sup>
	<b>BTG</b>	7/15 (46.7)	--	13/15 (86.7)	0.061 <sup>3</sup>
<b>Pain reduction over 1<sup>st</sup> half-hour (measured by SPID25 for Del studies, SPRID30 for BTG study)</b>	<b>Del</b>	0.29	0.53	0.60	<0.001 <sup>2</sup>
	<b>BTG</b>	0.9	--	1.8	0.085 <sup>3</sup>

<sup>1</sup>Proportion of responders analyzed by the Cochran-Mantel-Haenszel test for trend, which is equivalent to the general association chi-square test for the BTG clinical study; pain reduction analyzed with the linear trend contrast from analysis of variance model. (The analyses of the Del studies controlled for site.)

<sup>2</sup>The results statistically favored benzocaine within the three individual sites as well.

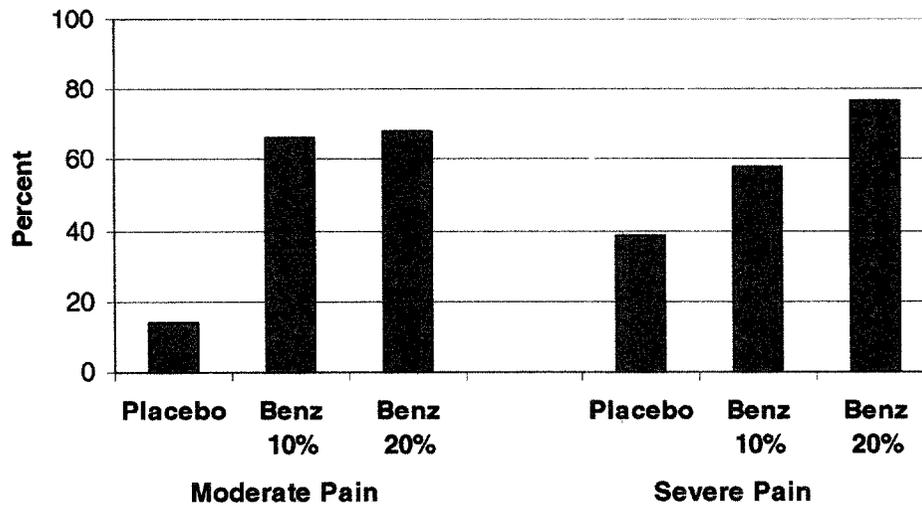
<sup>3</sup>The protocol-specified analysis in the BTG clinical study was the same that would be used in a pivotal study, in which randomization would be stratified by baseline pain. If this study were to be analyzed on its own, then due to the lack of stratification and the small sample size (15/group), the more appropriate analysis would not control for the baseline pain, resulting in significant p-values of 0.022 for proportion of responders and 0.037 for SPRID.

The Del studies showed virtually no dose response between benzocaine 10% and 20% among subjects with moderate pain at baseline, but a clear one (19% increase in the percent of responders) among subjects with severe pain at baseline, as seen in the following table.

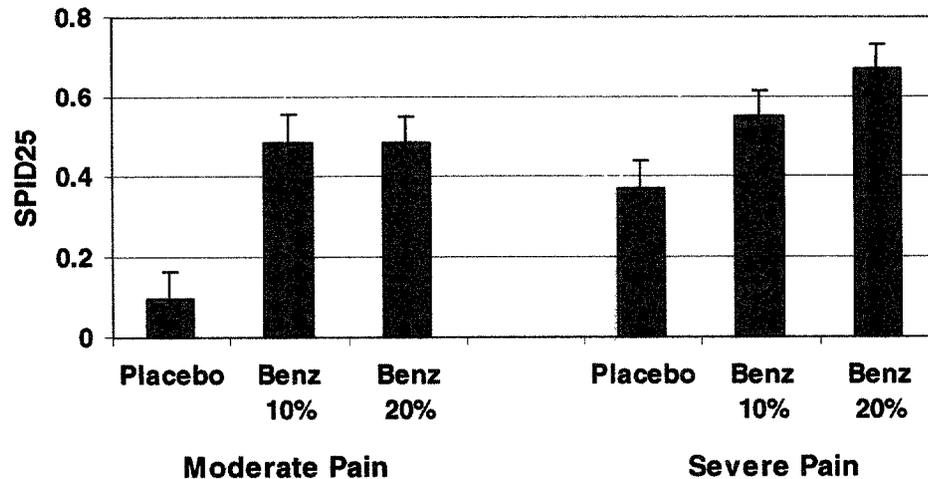
	Moderate Baseline Pain			Severe Baseline Pain		
	Benz 10% (n= 24)	Benz 20% (n= 25)	p-value	Benz 10% (n=52)	Benz 20% (n=43)	p-value
<b>Percent Responders</b>	66.7	68.0	0.922	57.7	76.7	0.052
<b>SPID25 (mean)</b>	0.48	0.49	0.967	0.55	0.67	0.197

Despite the small subgroup sample sizes, among subjects with severe baseline pain, the difference between the 10% and 20% benzocaine groups was marginally significant for the percentage of responders (the primary efficacy parameter). These results, as well as those for the placebo group, are shown in the following two figures.

**Figure 1. Percent Responders, by Moderate and Severe Baseline Pain**



**Figure 2. Mean SPID25 by Percent Benzocaine and Baseline Pain**



In summary, the similarities of the methods and results of the BTG clinical study to the Del clinical studies attest to the Del studies' validity. The BTG clinical study, when analyzed on its own, and the Del studies have proven benzocaine's effectiveness for toothache pain. Also, the Del studies showed a dose response between 10% and 20% benzocaine. Thus CHPA Benzocaine Task Group believes that the studies conducted to date satisfy the requirements for monograph status and that no additional studies are needed.

- 4. If the Agency requires an additional efficacy study with 10% and 20% benzocaine, does the Agency agree the attached protocol is adequate to demonstrate the efficacy for both 10% and 20% benzocaine-containing products and fulfills the requirement for one additional study as outlined in the feedback letter dated 29 October 2002?**

See attached protocol in Appendix V.