

MEETING MINUTES

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

Meeting Request Date: March 25, 2004
Meeting Package Submission: May 28, 2004
Meeting Date: June 28, 2004

Background

In the Oral Health Care proposed rulemaking, benzocaine is listed as Category III (meaning lack of data) for efficacy for the relief of toothache pain. This meeting is the latest in a series of communications between CHPA's Benzocaine Task Group and FDA regarding the effectiveness of benzocaine. CHPA proposed a research program for benzocaine that was described in a letter dated June 21, 2002. FDA responded in a feedback letter dated October 29, 2002. CHPA requested this meeting to discuss issues raised by FDA in that feedback letter. CHPA submitted a meeting package which included results of a pilot study, the proposed protocol to evaluate 10% and 20% benzocaine, and a proposed OTC label.

Meeting Attendees

FDA Division of OTC Drug Products

Charles Ganley, M.D.	Division Director
Curtis Rosebraugh, M.D., M.P.H.	Deputy Director
Debbie Lumpkins	Team Leader
Robert Sherman	IDS Reviewer
Elaine Abraham, R.Ph.	Project Manager
Andrea Leonard Segal, M.D.	Medical Team Leader
Jin Chen, M.D., Ph.D.	Medical Officer
Gerald Rachanow, P.D., J.D.	Regulatory Counsel

Division of Dermatology and Dental Drug Products

John Kelsey, D.D.S., M.B.A.	Dental Team Leader
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Division of Anesthetic, Critical Care, and Addiction Drug Products

Thomas Permutt, Ph.D.	Statistical Team Leader
Nancy Chang, M.D.	Anesthesia Team Leader
Arthur Simone, M.D.	Medical Officer

Consumer Healthcare Products Association

Douglas Ws. Bierer, Ph.D.	Vice President, Regulatory and Scientific Affairs
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Del Pharmaceuticals, Inc.

Charles J. Hinkraty	President
Serap Ozelkan, Ph.D.	Director, Pharmaceutical Research
Patricia Suita-Cruce, Ph.D.	Vice Pres. Pharmaceuticals, Research & Development
Randy M. Sloan	Senior Vice President, Marketing
William O. Thompson, Ph.D.	Professor and Director Emeritus of Biostatistics, Medical College of Georgia
William E. Cooley, Ph.D.	President, Cooley Consulting, Inc.

Wyeth Consumer Healthcare

Stephen A. Cooper, D.M.D., Ph.D.	Sr. V.P., Global Clinical and Medical Affairs
Margaret S. Hughes, Ph.D.	Associate Director, Regulatory Affairs
Sudam M. Pathirana, Ph.D.	Clinical Research Scientist
Alan H. Stokes, Ph.D., D.A.B.T.	Senior Manager, Regulatory Affairs
Joel Waksman, Ph.D.	Assistant Vice President, Biostatistics and Data Management

Other Participants

Frank A. Kyle, D.D.S., M.S.	American Dental Association
Daniel Healey	FDC Reports – Tan Sheet

Meeting Minutes

Dr. Bierer (CHPA) opened the meeting with a brief presentation of the key issues that have been addressed by the current submission. He noted the agency concerns were on the need for clear directions on applying the correct amount of benzocaine, frequency of dosing, methemoglobinemia, efficacy, and dose response of the 10% and 20% formulations. The Benzocaine Task Group's conclusions on the data submitted for the meeting were as follows:

- The revised labeling provides clear directions for use
- The Del studies indicate a directional difference between 10% and 20% benzocaine
- The pilot clinical study reaffirmed the results of the Del studies and validated the methodology
- Methemoglobinemia is exceedingly rare – no labeling should be required

The questions listed below were provided by CHPA and discussed at the meeting. It was agreed that FDA would reconsider the points made by CHPA and include an addendum of some of the FDA responses in the minutes.

1. Does the Agency agree with the proposed OTC labels (Del Pharmaceuticals and Wyeth Consumer Healthcare) for benzocaine-containing products marketed for toothache?

FDA Response:

Since the primary outcome variable measures an improvement of one category on the pain scale, we believe the results will not support “relief of pain” as the proposed label currently states. The results will support “reduction in toothache pain.”

Therefore we have the following recommendations:

- The most likely supportable statement of identity for the Del product would be “agent for the reduction of toothache pain” or “toothache pain reducer”.
- The most likely supportable statement of identity for the Wyeth product would be the same statements above for the Del product and “oral anesthetic”.
- Both products should have the additional warning:

Warnings: “See a dentist as soon as possible whether or not the pain is relieved. Toothaches and open cavities indicate serious problems that need prompt attention.”

Addendum:

An additional statement of identity for the Wyeth product that was not discussed at the meeting is "oral anesthetic/analgesic". Any suggested wording for the statement of identity of the product or other labeling, such as the methemoglobinemia warning, will be resolved in the rulemaking and may be dependent on comments already filed in the docket.

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

FDA Response:

The directions appear to be clear; however the information from the pilot study was limited to 30 subjects. Although the majority used the correct amount, one of these subjects used an excessive amount. If the results from this study are reflective of the use by an OTC population, then several percent of the population are likely to use excessive amounts. It would be helpful to understand why these outliers (such as the subject who used >1600 mg) exceed the recommended amount.

If we determine that the pictogram is necessary for correct use of the product, then we would have to consider an exemption for the drug facts labeling to include a pictogram.

Similar directions (pictogram) should be used for the pivotal efficacy trial as would be anticipated for the marketed product.

We are not aware of any actual use data that demonstrate how these products are used in the OTC setting. If the amount of product refers also to the frequency of use, we do not have any data on the clarity of the directions.

Addendum:

In comment 44 of the preamble to the OTC labeling final rule (64 FR 13254 at 13271, March 17, 1999), the agency notes that the use of symbols and pictograms will remain voluntary provided their use is not a substitute for required OTC drug product labeling. Consequently, it is important to understand if CHPA believes that the pictogram is necessary to determine the appropriate amount of product to use. There are several issues to consider. If the pictogram size should be standardized to show the actual amount to be used, then it should probably be specifically described in any future rulemaking in the codified section. Then, it must be determined whether

the pictogram should be optional or required in labeling. Finally, the location of the pictogram would have to be determined, as the agency has stated that graphical images must not interrupt the required information panel or panels (64 FR 13254 at 13266).

- (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?**

FDA Response:

The dosing regimen will be determined after the pivotal efficacy clinical trial report is submitted and reviewed. The results from the pilot study have not been completely reviewed. One of the issues for consideration is whether the two-hour time frame is supported by the data from the pilot study and the proposed efficacy study. One of the things we will be looking at is the number of subjects who require rescue medication in less than two hours. If a significant number require rescue before the next scheduled dose, one would question the two-hour frequency. In the OTC setting, consumers who need rescue before two hours are likely to dose prior to the two-hour time frequency.

Discussion:

Noting that the effect for the majority of subjects lasted two hours, CHPA asked what time frame is reasonable. FDA noted that because four of 15 subjects required rescue before two hours, this time frame needs to be justified. FDA stated that alternative labeling may help inform consumers what to do if no relief is seen within two hours.

2. **Based on our review of the updated safety assessment 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?**

FDA Response:

The product label should include a warning regarding the possibility of methemoglobinemia occurring with topical application, especially in children and other at risk populations. Many of the assumptions about the safety rely on using the recommended amount. There is a smaller margin of error in young children. We also have concerns about the excessive use of the product by people who do not get relief. There are a sufficient number of cases of methemoglobinemia reported in subjects who receive a single dose of benzocaine spray. The failure to have reports for the

topical oral products in the AERS database does not sufficiently reassure us that it does not occur in the OTC setting.

Discussion:

CHPA reiterated that reports of methemoglobinemia have been rare. They suggested that FDA is basing its call for a warning on a theoretical concern. If there was a serious side effect, it would be noticed. FDA stated that it is reassuring that there are few cases of methemoglobinemia reported. However there is the concern of under reporting of OTC products. The product is safe if used properly, but a warning would give consumers a sense of the consequences if the product is not used correctly. Since it is labeled for use down to age two, there are concerns about children, especially children of small stature and also concerns in the elderly and in those with cardiovascular problems. CHPA asked how the warning would be stated. FDA replied that it would be in the context of describing the condition of methemoglobinemia.

- 3. Does the Agency agree that the results from clinical study BZ-03-08, in conjunction with results of previous Del clinical studies 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?**

FDA Response:

We do not agree that the results of the pilot study in conjunction with the previous Del studies are sufficient to establish effectiveness. As described in FDA's letters dated July 28, 1998 and October 29, 2002, we expressed concerns about the deficiencies of the prior studies. During the meeting of June 3, 2002, we made several comments about what needed to be successfully demonstrated for reaching the conclusion about efficacy of benzocaine. The results of this pilot study support the objectives of the study, which include verifying the methodology and examining subject compliance with directions. However, at that meeting, we commented that information would be needed to support the efficacy of both the 10% and 20% strengths of benzocaine, which would require that both products be tested in a single trial and a dose response established.

Discussion:

CHPA stated that there have been three separate Del studies plus the pilot study demonstrating effectiveness. The Del studies showed a good dose response in patients with severe pain at baseline. CHPA agreed that there were flaws in the Del

studies as FDA had previously pointed out. However, these flaws were corrected in the pilot study, which resulted in similar findings to the Del studies, lending credibility to the Del studies. CHPA believes that the pilot study should be accepted as pivotal and further studies are not required. FDA stated that there was no 10% benzocaine group in the pilot and the results were not statistically significant. The Agency is not convinced that effectiveness has been established and reiterated the fact that another study is necessary.

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 fulfils the requirement for one additional study as outlined in the feedback letter dated 29 October 2002?

FDA Response:

- a) The dose-response demonstration appears to be a very low hurdle to win as proposed: There are multiple opportunities to win in the current scheme, beginning with a test of the primary outcome variable in the total population and extending to subgroup testing in two secondary outcome variables. In past studies of benzocaine, no demonstration of the superiority of the 20% product to the 10% product was achieved until the baseline severity was considered. Your conclusion was that the 20% product was more effective than the 10% product in subjects with high baseline pain scores; but that in subjects with mild to moderate entry pain, there was no advantage of the 20% strength over the 10% one. It would make more sense to set up this pivotal study analysis in the same way – the labeling would then reflect the appropriate strength product for the appropriate consumer.

Discussion:

CHPA stated that the study was looking at a one-unit improvement over two successive time points. Based on these criteria, approximately 87% of Del subjects responded versus 47% of placebo. They asked if in acute toothache, shouldn't a one-unit drop be considered relevant? FDA noted the problem is primarily with the time frame of five minutes for a one-unit improvement. Also if 20% shows value in severe pain, possibly the benzocaine products should be labeled for use in mild or severe pain. CHPA stated that 20% products are differentiated on the label from 10% as "maximum strength". FDA agreed to discuss this issue further internally.

Addendum:

The criteria for demonstration of a dose response need to be clarified. For example, if the duration of effect for benzocaine 10% is 10 minutes and for benzocaine 20%, 10 minutes and 30 seconds (5% increase), does this demonstrate a dose response? As stated at the meeting, we do not think this alone would be an adequate demonstration of dose response and would require more supportive evidence. Similar comments were made for the "Time to onset of meaningful relief" criteria. The section on establishment of a dose response relationship needs to be clarified.

- b) The protocol proposes enrolling only subjects who are 18 years and older; however, the proposed label in this submission states "for adults and children ages 2 and older." Since this drug will be available OTC and has utility for children, this group should be considered for enrollment. The entrance criteria also exclude pregnant or breast-feeding women. The labeling you have proposed does not include any restrictions on use in pregnant or breast-feeding women. Unless there is a specific reason to exclude them, they should be allowed to enroll.

Discussion:

The CHPA Task Group asked if it would be acceptable to enroll patients 12 and older. They noted that is corporate policy not to include pregnant subjects. Also, they would have trouble finding pregnant women. This can possibly be handled in the labeling.

Addendum:

After internal discussion on that question, we agree that it would be acceptable to enroll patients only down to age 12. You are encouraged to enroll a sufficient number of pediatric patients so that they comprise at least 20% of the total enrollment. They should not be clustered at the higher pediatric ages (e.g. at least 30% of the pediatric patients should be in the 12-14 age range).

- c) For the Dental Pain Scale, rather than subjects being asked "What is your starting pain" at baseline, it would be more consistent to ask the question the same way during the first evaluation as it is during subsequent evaluations, for which you have proposed, "How much pain do you have at this time?"
- d) In the protocol, it states that a VAS is used to measure baseline pain; however, there is no further mention in the protocol or data analysis sections of any use of these VAS measurements.

Discussion:

CHPA explained that the VAS measurement at baseline was to assure, in combination with the Dental Pain Scale measurement, that the patient did have a significant degree of pain prior to enrollment.

Addendum:

The purpose of the VAS measurement at baseline should be described in the protocol.

- e) The duration of effect is listed as a secondary efficacy endpoint – however, if the pain relief only lasts for a clinically insignificant time, this may be an issue in the assessment of benzocaine’s efficacy.
- f) Justify limiting your pain evaluation to 120 minutes.

Discussion:

CHPA stated that the pain evaluation was limited to 120 minutes for practical reasons. Patients would be enrolled in clinics at dental schools and if enrolled late in the day might not have time for follow-up beyond 120 minutes.

Addendum:

After further discussion, we agree that pain evaluation limited to 120 minutes is acceptable.

- g) We need clarification about the censoring of premature dropouts. Some dropouts are censored but others are not. Please clarify under which circumstances dropouts would not be censored.

Discussion:

CHPA clarified that dropouts would be censored if they used rescue medication. The score at the time of dropout or at baseline would be carried forward, whichever was worse.

- h) Is the placebo the vehicle of the benzocaine product?

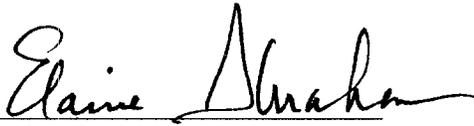
Discussion:

CHPA clarified that the placebo is a true vehicle.

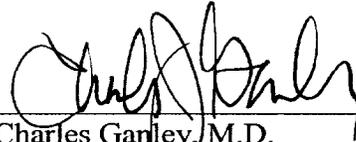
CHPA acknowledged that a five-center study with 500 patients would be a major undertaking, which they would like to be the final study on benzocaine. FDA stated that the sponsor was encouraged to submit a revised protocol that we would consider treating as a special protocol assessment.

Addendum:

Given that this is an important study, it is worthwhile for FDA to review changes to a protocol so there is no misunderstanding of communications.



Elaine Abraham
Minutes Preparer



Charles Ganley, M.D.
Concurrence