



founded 1881

September 5, 2008

M. Scott Furness, Ph.D., Director
Division of Nonprescription Regulation Development
Office of Nonprescription Products
Center for Drug Evaluation and Research
United States Food and Drug Administration
Department of Health and Human Services
10901 New Hampshire Avenue
WO Building 22, Room 5411
Silver Spring, MD 20993

Re: Oral Health Care Drug Products for Over-the-Counter Human Use; Antigingivitis/
Antiplatelet Drug Products; Establishment of a Monograph; Proposed Rules;
[Docket No. 1981N-0033P]

Dear Dr. Furness:

On May 7, 2008, the Consumer Healthcare Products Association (CHPA) received correspondence from the United States Food and Drug Administration (FDA) requesting safety data for over-the-counter (OTC) mouthrinse products containing cetylpyridinium chloride (CPC). CHPA, founded in 1881, is a national trade association representing manufacturers and distributors of over-the-counter medicines and dietary supplements. The agency's correspondence was circulated to CHPA members. The following companies (listed alphabetically) collectively responded to FDA's request for data:

- Church & Dwight Company, Inc.
- Colgate Palmolive Company
- GlaxoSmithKline Consumer Healthcare
- Johnson & Johnson Healthcare Products Division of McNEIL-PPC, Inc.
- The Procter & Gamble Company

The FDA requested adverse event reports associated with OTC CPC-containing mouthrinses for tooth-staining and/or oral irritation, as well as reports for all other adverse events, from the

**Consumer Healthcare
Products Association**
900 19th Street, NW, Suite 700
Washington, DC 20006
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previous ten years. The aggregate data submitted by the five companies listed above are provided in Table 1. The data presented here do not include any safety information submitted directly to the agency by other companies that market or previously marketed OTC CPC-containing mouthrinses.

Summary of Data

During the past 10 years, approximately 119,302,340 over-the-counter mouthrinse product units containing CPC have been shipped domestically by the five companies listed above. The strength of CPC in these OTC products ranged from as low as 0.03% CPC [used as an inactive ingredient (*i.e.*, preservative)] to as high as 0.10% CPC. These companies reviewed their internal databases for adverse event reports (AERs) for the past 10 years, or when applicable, the period of time for which the product was shipped, using accepted MedDRA terms. Review periods ranged from 1 to 10 years.

The total number of AERs received was 6239 of which 6231 (99.9%) were non-serious. Oral irritation accounted for 32.3% of the total reports (2014 cases); tooth discoloration accounted for 36.3% (2262 cases); and “other” adverse events accounted for 33.4% (2083 cases)¹. Overall findings from the safety review are provided in Table 1 below. Rate of occurrence was calculated based on the number of events per units shipped. The adverse event reports were not evaluated for causality so the data contained in this submission do not imply a causal relationship between the adverse event/s reported and the use of these OTC mouthrinse products.

The rates of occurrence were similar for the various products and do not appear to indicate a safety concern. The ranges of rate of occurrence for all product strengths were as follows:

Overall:	0.00020 - 0.01762
Oral Irritation:	0.00000 - 0.00692
Tooth Discoloration	0.00000 - 0.00208
Other Events	0.00004 - 0.01053

It should be noted that the underlying disease state for which these OTC mouthrinses are used (*i.e.*, reduction or prevention of gingivitis and dental plaque²) can be characterized by oral irritation, potentially confounding the rate of occurrence reflected in these data. Also, the background rate of occurrence for oral irritation and tooth discoloration for non-users is unknown but would be useful to provide proper context to the data.

¹ There were 120 cases which included reports of both oral irritation and tooth discoloration. These cases were included in both “oral irritation” and “tooth discoloration” categories but were not included under “other.”

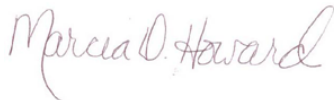
² There was one individual safety review conducted on OTC CPC-containing mouthrinse products which are used to alleviate dry mouth conditions that has been included in this summary report.

Conclusions

The five manufacturers of OTC cetylpyridinium chloride-containing mouthrinses listed above conducted a safety review of adverse event reports received within the last 10 years using accepted MedDRA terms. OTC products containing four different strengths of CPC, including CPC used as an inactive ingredient, were included in the review with both serious and non-serious adverse events reporting oral irritation, tooth discoloration, and other adverse events assessed. Serious adverse events were defined as outlined in the Dietary Supplement and Nonprescription Drug Consumer Protection Act of 2006³ and comprised a small percentage of the overall adverse event reports (0.1%). Therefore, it does not appear there is a public health issue based on the data provided.

Please feel free to contact us if we can be of further assistance.

Sincerely,



Marcia D. Howard, Ph.D.
Director, Regulatory & Scientific Affairs



David C. Spangler, Esq.
Senior Vice President, Policy and International Affairs

cc: Robert Sherman, Division of Nonprescription Regulation Development
FDA Office of Nonprescription Products

Elizabeth H. Anderson, Esq.
Personal Care Products Council

MDH/09-05-08

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³ One company used the International Conference on Harmonisation (ICH) definition for seriousness.

Table 1: Summary of Adverse Event Reports from Use of Over-the-Counter Cetylpyridinium Chloride-Containing Mouthrinses⁴

Individual Safety Review ⁵	Product Strength	Product Units Shipped	Total Number of Cases	Number of SAEs	Number of Non-SAEs	Rate of Occurrence (Overall)	Number of Oral Irritation Cases	Rate of Occurrence (Oral Irritation)	Number of Tooth Discoloration Cases	Rate of Occurrence (Tooth Discoloration)	Number of Other Cases	Rate of Occurrence (Other Cases)
1 ⁶	0.03%	1,718,288	37	0	37	0.00215	9	0.00052	11	0.00064	17	0.00099
2	0.05%	1,235,502	4	0	4	0.00032	3	0.00024	0	0.00000	1	0.00008
3	0.05%	5,084,000	10	0	10	0.00020	6	0.00012	2	0.00004	2	0.00004
4	0.05%	20,000	2	0	2	0.01000	1	0.00500	0	0.00000	1	0.00500
5 ⁶	0.05%	3,020,000	532	7	525	0.01762	209	0.00692	5	0.00017	318	0.01053
6	0.07%	107,870,000	5649	1	5648	0.00524	1786	0.00166	2241	0.00208	1742 ⁷	0.00161
7	0.10%	125,010	1	0	1	0.00080	0	0.00000	0	0.00000	1	0.00080
8	0.10%	229,540	4	0	4	0.00174	0	0.00000	3	0.00131	1	0.00044
Total	--	119,302,340 ⁸	6239	8	6231	--	2014	--	2262	--	2083	--

Table 1 reflects adverse event reports received by nonprescription drug manufacturers during the past 10 years (May 1998 – May 7, 2008⁸), or the period for which the product was shipped (if appropriate), associated with the use of over-the-counter (OTC) cetylpyridinium chloride (CPC) containing mouthrinse products⁴. SAEs represent serious adverse events as defined in the Dietary Supplement and Nonprescription Drug Consumer Protection Act (effective December 22, 2006³). Non-SAEs reflect non-serious adverse events.

⁴ The adverse event reports were not evaluated for causality so the data do not imply a causal relationship between the adverse event/s reported and the use of these OTC mouthrinse products.

⁵ One company submitted two separate safety reviews and one company submitted three separate safety reviews based on their respective product lines.

⁶ CPC used as an inactive ingredient (preservative).

⁷ Number of “other” cases reflects all cases *not* involving oral irritation or tooth discoloration. There were 120 cases reporting both oral irritation and tooth discoloration that were included under the individual categories of oral irritation and tooth discoloration.

⁸ Data includes 354,550 products shipped through August 21, 2008.