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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, rm 1061
Rockville, MD 20852

RE: Docket No. 81N-033P – Oral Health Care Drug Products for Over-the Counter Human Use: Antigingivitis/Antiplaque Drug Products; Establishment of a Monograph: Proposed Rules

To Whom It May Concern:

These comments are submitted by Colgate-Palmolive Company (Colgate) in response to the May 29, 2003 Federal Register publication (Advanced Notice of Proposed Rulemaking (ANPR) in which the Food and Drug Administration (FDA) requested information and comments to the Docket based on their intention to establish conditions under which over-the–counter (OTC) drug products for the reduction or prevention of dental plaque and gingivitis are generally recognized as safe and effective and not misbranded.

In this ANPR, the Dental Plaque Subcommittee determined that Sanguinaria Extract is safe for use in oral rinse and dentrifrice products at 0.03 to 0.075 percent concentration. The Subcommittees' decision was based on the large margin of safety between levels of human exposure and adverse effect levels found in animals.

Colgate-Palmolive Company would like to present an additional publication in support of the Subcommittees' conclusion entitled "Viadent Usage and Oral Leukoplakia: A Spurious Association" (Attachment 1). This report is presented to address the post 1990 Call for Data publication of three studies alleging a relation between sanguinaria and oral leukoplakia. It is our opinion that the attached manuscript addresses the safety concerns raised in these articles.

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The toxicological profile of sanguinaria is well characterized and the preclinical data supporting its safe use in humans include a battery of genotoxicity studies, two carcinogenicity studies, and numerous mucous membrane irritation studies in hamsters, dogs and rats. In addition, three human studies, as well as two oral sensitization studies support the safety of sanguinaria in oral care products.

Since 1998, three studies alleging a relation between sanguinaria and oral leukoplakia have been published; however, none of these papers fully satisfy the criteria used in epidemiology for establishing causation. These authors never determined whether exposure took place prior to the onset of illness, supported the reliability of the questionnaire used to identify cases and controls, or provided the basis of the statistical analysis used. In an article entitled "The Association Between Viadent Use and Oral Leukoplakia- Results of A Matched Case-control Study (Ana K. Mascarenhas, Carl M. Allen, and Melvin L. Moeschberger in the Journal of Public Health Dentistry 2002; 62: 158-162), statistical significance was shown between the number of cases using a sanguinaria containing oral care product and the number of controls who used such a product. Statistical significance is minimal and is lost with very small changes in the numbers. If one less person from among the 58 cases reported that they used a sanguinaria containing oral care product (26 of 58 instead of 27 of 58), there would be no statistically significant difference between the number of sanguinaria containing oral care products users who developed leukoplakia and those who did not. Similarly, if one more person from among the 58 controls (18 of 58 instead of 17 of 58) reported having used a sanguinaria containing oral care product, there would be no statistically significant difference between the users who developed leukoplakia and those that did not. Furthermore, the results of this study were based on cases already included in two earlier papers, but were compared to a different set of controls. As a result, these findings are invalid and should not be considered in the overall safety evaluation of sanguinaria.

Should the Agency have any questions regarding this comment, please do not hesitate to contact me.

Respectfully,

Eugenie C. Acosta

Ms. Eugénie C. Acosta