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

RE: Comments on *Oral Health Care Drug Products for Over-The-Counter Human Use: Antigingivitis/Antiplaque Drug Products; Establishment of a Monograph*, 68 Fed Reg. 32232-32287.

Docket No. 81N-033P

Dear Sir/Madam:

The American Dental Association (ADA or Association) is pleased to provide the FDA with comments regarding the proposed rule: *Oral Health Care Drug Products for Over-The-Counter Human Use: Antigingivitis/Antiplaque Drug Products; Establishment of a Monograph*. The ADA represents over 147,000 dentists in the United States and seeks to advance the art and science of dentistry, promoting high quality dental care and the oral health of the American public.

Summary of Proposed Rule

The FDA has issued this advance notice of proposed rulemaking (ANPR) 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. The ANPR contains the unaltered conclusions and recommendations of the independent Dental Plaque Subcommittee of the Nonprescription Drugs Advisory Committee of the Center for Drug Evaluation and Research ("Subcommittee") and the FDA's preliminary comments on them. FDA is publishing this ANPR solely to stimulate public discussion and comment. It does not represent the FDA's position on any particular matter covered in the ANPR.

The Subcommittee held a number of meetings from August 1993 to December 1998. The ADA provided testimony on several occasions. The resulting ANPR is generally consistent both with the ADA's testimony and with the ADA Guidelines for the Acceptance of Chemotherapeutic Products for the Control of Supragingival Plaque and

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C21

Gingivitis (J. Am. Dent. Assn., Vol. 112, April 1986, pgs 529-532) that were current for most of these hearings. They are also consistent with the Sept 1997 update titled, ADA Guidelines for Chemotherapeutic Products for Control of Gingivitis. However, the Association does wish to comment on certain specific aspects of the ANPR.

ADA Comments

P32232 – 32234 Supplementary Information

Combination Products

Subcommittee Recommendation: The Subcommittee believes that it is rational to combine an anticaries agent and/or a desensitizing agent with a Cat I antigingivitis/antiplaque agent. The FDA is dissenting from this Subcommittee recommendation, because no such combination products were submitted for the OTC review. The FDA is requesting supporting data and information demonstrating that these combination products can generally be recognized as safe and effective for OTC use.

ADA Comment: The ADA concurs with the Subcommittee's recommendation that these are rational combinations. The ADA also agrees with the FDA that supporting data and information should be submitted demonstrating that specific combination products are safe and effective for all indications.

Antigingivitis or/and Antiplaque Claims

Subcommittee Recommendation: The Subcommittee concluded that an active ingredient could be either an antigingivitis agent alone or an antigingivitis/antiplaque agent. It also stated that the therapeutic endpoint for both antigingivitis and antiplaque active ingredients is a significant reduction in gingivitis. During its meetings, the Subcommittee also concluded that an agent that only reduced plaque, but not gingivitis, should not be able to make an antiplaque claim.

ADA Comment: The ADA strongly agrees with the Subcommittee's position that to be able to make either an antigingivitis or and antiplaque claim, a product must be able to demonstrate it can cause a significant reduction in gingivitis. The ADA emphasizes the importance of removing plaque daily for maintaining gingival health because plaque is the etiologic agent for gingivitis. Not all plaque is located at the gingival margin, however, and it is possible that a product could have an effect to reduce plaque without having an effect on gingival health.

OTC Antigingivitis Drug Product Ingredients

Subcommittee Recommendation: The Subcommittee agreed that ingredients that work to decrease gingivitis by means other than plaque reduction would be inappropriate to use in OTC antigingivitis drug products. They felt that these products might mask the symptoms of a more serious condition. The FDA states that the Subcommittee agreed that none of the submitted ingredients worked by any mechanism other than plaque reduction, so the issue was not discussed further.

ADA Comment: One of the Cat I active ingredients, 0.454% stannous fluoride, has as its proposed antigingivitis mechanism a decrease in plaque bacteria metabolism rather than killing plaque bacteria to decrease plaque mass. Indeed, one of the tests that is proposed for OTC 0.454% stannous fluoride antigingivitis products, called the plaque glycolysis and regrowth method (PGRM), measures plaque metabolic activity and not plaque mass. On this page, the FDA also indicates that the subcommittee is recommending a special antigingivitis reduction only claim for 0.454% stannous fluoride products because plaque mass is not reduced. It is, therefore, unclear why the Subcommittee concluded in the FDA reports, that none of the submitted antigingivitis agents worked by a mechanism other than plaque reduction. The ADA believes that agents that reduce gingivitis by either killing plaque bacteria or by reducing its metabolic activity should be permitted in OTC antigingivitis products.

ADA's Assistance

Subcommittee Recommendation: The Subcommittee gave recognition of the ADA's assistance in providing data, information and testimony during the course of the Subcommittee's hearings. The Subcommittee also acknowledged receipt from the ADA of the ADA Guidelines for the Acceptance of Chemotherapeutic Products for the Control of Supragingival Plaque and Gingivitis (April 1986), for consideration in making its recommendations on the requirements for safe and effective OTC antigingivitis/antiplaque products.

ADA Comment: The ADA was pleased to provide assistance to the Subcommittee. The April 1986 ADA Guidelines for the Acceptance of Chemotherapeutic Products for the Control of Supragingival Plaque and Gingivitis outline the clinical testing that the ADA believes is necessary to demonstrate the safety and effectiveness of novel chemotherapeutic products for the control of plaque and gingivitis. The Subcommittee referred to these guidelines when it evaluated the studies submitted in response to the FDA's Sept 19, 1990 request for data and concluded that the data supported Category I status for only three active agent/active agent combinations.

In the ADA's efforts to continually assure that its product evaluation guidelines reflect current scientific understanding, it periodically reviews and updates these guidelines. An update to the April 1986 gingivitis guidelines titled, ADA Acceptance Program Guidelines for Chemotherapeutic Products for the Control of Gingivitis, was published in Sept 1997. When the April 1986 guidelines were reviewed, it was concluded that the required safety and efficacy studies should be retained. However, the 1997 update reflects an effort by the ADA's Council on Scientific Affairs to put all ADA guidelines into a standardized format, and also includes suggested clinical protocol guidelines that companies can follow to demonstrate safety and effectiveness. The April 1986 guidelines are still referenced in the Sept 1997 update for such things as the ADA position on plaque and gingivitis, and for testing requirements for microbiology and toxicology. A copy of the Sept 1997 update is included with these comments.

The FDA may wish to refer to these updated guidelines if it decides to evaluate additional antigingivitis agents in this OTC review. The updated guidelines may also be useful after

the final FDA monograph on OTC antiplaque/antigingivitis products is published, when all future antigingivitis agents will need to go through the New Drug Approval process.

Pg 32234, I. Submission of Data and Information

Chlorhexidine Digluconate

FDA Comment: The FDA states that chlorhexidine digluconate was among ingredients that “were not marketed for a material time and to a material extent for antigingivitis/antiplaque use in the United States”.

ADA Comment: Point of clarification – If the FDA meant to say that chlorhexidine has not been marketed for a material time and to a material extent for antigingivitis/antiplaque use in the United States in an OTC product, the ADA concurs. However, 0.12% chlorhexidine digluconate has met these conditions as a prescription product, and there exists a significant amount of published data on the safety and effectiveness of this ingredient as an antigingivitis/antiplaque agent.

Pgs 32235-32238, II General Statements and Recommendations, B. Background and General Discussion of Terms

Definitions

Subcommittee Recommendation: The subcommittee has recommended definitions for the following terms: calculus/tartar, dental plaque, gingival sulcus, gingivitis, oral hygiene, pellicle, and periodontitis, and reached certain conclusions about the relationship of dental plaque to gingivitis.

ADA Comment: The ADA agrees with the definitions presented in this section, and with the Subcommittee’s conclusions about the relationship of dental plaque and gingivitis, especially the conclusion that “gingivitis reductions must be measured directly”. This refers to the possibility that some agents might be able to reduce plaque while not reducing gingivitis. The ADA does not support approving products as antigingivitis agents if they have only been demonstrated to reduce plaque.

Pgs 32238-32239, II General Statements and Recommendations, C. Drug/Cosmetic Status

Antiplaque Claims

Subcommittee Recommendation: The Subcommittee concludes that any reference to the control of dental plaque should be interpreted as a drug claim, and that a product making an antiplaque claim must demonstrate a clinically significant reduction in gingivitis.

ADA Comment: The ADA agrees with the Subcommittee that a product that can reduce plaque but that does not have an effect on gingivitis may mislead people into thinking that the plaque reduction is therapeutically significant, when it may not be. Therefore,

whenever a plaque claim is made, the ADA agrees with the Subcommittee that the product should also be required to show that it is effective in reducing gingivitis.

Supragingival Tartar Buildup

Subcommittee Recommendation: The Subcommittee concludes that any reference to supragingival tartar (calculus) should be interpreted as a cosmetic claim. The Subcommittee did not make reference to subgingival tartar.

ADA Comment: The ADA agrees with the Subcommittee. In all clinical studies to date, OTC products that help prevent supragingival tartar buildup have not demonstrated any beneficial effect on gingival health. In addition, none of these products have been shown to have any effect on subgingival tartar.

Pg 32240, General Statements and Recommendations, E. Combining Drug Products

Subcommittee Recommendation: The Subcommittee outlines its rationale for why it believes certain combination antigingivitis drug products are rational.

ADA Comment: The ADA concurs with the subcommittee comments.

Pg 32240, General Statements and Recommendations, F. Testing of Antigingivitis/Antiplaque Products

Subcommittee Recommendation: The Subcommittee concludes that products using the three recommended Cat I OTC antigingivitis/antiplaque agents should be required to demonstrate their effectiveness through a series of final formulation tests, using the specific marketed product formulation and dosage form (i.e. dentifrice, gel, paste or rinse).

ADA Comment: The ADA concurs with this recommendation. Because other ingredients added to a formulation can modify active agent activity, the ADA believes that it is always necessary to test the final marketed product, rather than just the ingredient.

Pg 32240, General Statements and Recommendations, F. Testing, 1.Changes in Traditional Dosage Forms

Subcommittee Recommendation: The Subcommittee recommends that drug products containing Cat I active ingredients formulated in dosage forms other than those reviewed by the Subcommittee be required to demonstrate antigingivitis/antiplaque efficacy by a single 6-month, randomized, controlled clinical study.

ADA Comment: The ADA concurs with this recommendation, and would suggest that such clinical studies be designed as indicated in the ADA Guidelines for Chemotherapeutic Products for the Control of Gingivitis (Sept 1997). Different dosage forms may affect the duration or extent of contact with the active agent, which, in turn, may affect product efficacy.

Pg 32240, General Statements and Recommendations, F. Testing, 2. Final Formulation Testing

Subcommittee Recommendation: The Subcommittee is recommending that the PGRM to measure biological activity be a required for the Cat I active agents cetylpyridinium chloride and stannous fluoride, but not for the fixed combination of 0.92% eucalyptol, 0.042% menthol, 0.06% methyl salicylate, and 0.064% thymol rinse.

ADA Comment: It is unclear why this test would be required for only two of the active agents/active agent combination, or why it would be required for agents that act by killing plaque bacteria rather than by decreasing plaque metabolism.

Pg 32240, General Statements and Recommendations, F. Testing, 2. Final Formulation Testing

Subcommittee Recommendation: The Subcommittee is recommending that a disk reduction assay be included for the Cat 1 active cetylpyridinium chloride to demonstrate the availability of the active agent.

ADA Comment: It is unclear why this test would be required for only one of the Cat 1 active agents/active agent combination.

Pg 32241, General Statements and Recommendations, F. Testing, 2. Final Formulation Testing

Subcommittee Recommendation: The Subcommittee is recommending that a 2-week in vivo experimental gingivitis study be required for products with the fixed combination of 0.92% eucalyptol, 0.042% menthol, 0.06% methyl salicylate, and 0.064% thymol rinse, but not for products containing the other two Cat 1 active agents.

ADA Comment: It is unclear why this in vivo test would be required for only one of the Cat 1 active agents/active agent combinations. In fact, this type of test would not fall under Final Formulation Testing, but instead describes clinical testing.

Pg 32243, General Statements and Recommendations, H. Safety and Effectiveness, 2a. Safety, i. Toxicological Studies

Subcommittee Recommendation: The Subcommittee recommends that manufacturers conduct a variety of toxicological studies to demonstrate that an active agent is safe.

ADA Comment: The ADA concurs with this recommendation, as outlined in the ADA Guidelines for Chemotherapeutic Products for the Control of Gingivitis (Sept 1997).

Pg 32245, General Statements and Recommendations, H. Safety and Effectiveness, 2a. Safety, iv Microbiologic Evaluation

Subcommittee Recommendation: The Subcommittee recommends that manufacturers monitor plaque bacteria for 6 months of product usage to determine whether opportunistic or pathogenic organisms flourish, or whether microbial resistance develops.

ADA Comment: The ADA concurs with this recommendation, as outlined in the ADA Guidelines for Chemotherapeutic Products for the Control of Gingivitis (Sept 1997).

Pg 32246, General Statements and Recommendations, H. Safety and Effectiveness, 2c Clinical Trials, v. Interpretation of Data

Subcommittee Recommendation: The Subcommittee starts to address the issue of clinical significance by stating that clinical importance should be addressed in addition to statistical significance. However, the Subcommittee does not indicate how this is to be done, and concludes that the question of clinical significance remains unanswered.

ADA Comment: Many of the ideas expressed in this section are in agreement with those contained in the ADA's April 1986 and Sept 1997 gingivitis guidelines. The ADA concurs with the Subcommittee recommendations that reflect the ADA guidelines. Regarding the issue of clinical significance, the ADA Sept 1997 gingivitis guidelines addresses minimal effectiveness levels to establish clinical significance. Although these levels are subjective, they represent the concurrence of a large number of researchers. The ADA suggests that the FDA consider including some measure of clinical significance in the final rule.

Pg 32285-32287, Part 356-Oral Heal Care Drug Products for OTC Human Use

Subcommittee Recommendation: The Subcommittee makes several recommended changes to 21 CFR part 356.

ADA Comment: It is not clear if these recommendations are made by the Subcommittee or by the FDA. However, they appear to be the Subcommittee's recommendations, since combination active ingredients are being proposed as acceptable for OTC marketing. Once again, the ADA concurs. Previous ADA comments on this Subcommittee report already address other issues in this section.

The ADA appreciates the FDA's consideration of our comments. Should you have any questions, please contact Jonathan B. McLeod, Manager, Legislative and Regulatory Policy at (202) 789-5176.

Sincerely,



Eugene Sekiguchi, D.D.S.
President



James B. Bramson, D.D.S.
Executive Director

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