

CHURCH & DWIGHT CO., INC.

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October 27, 2005

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1051
Rockville, MD 20852

Re: Docket No. 2005D-0240
Draft Guidance for Industry on
Gingivitis: Development and
Evaluation of Drugs for
Treatment or Prevention

Church & Dwight Co., Inc. appreciates the opportunity to provide its views on FDA's draft guidance on the development and evaluation of drugs for prevention or treatment of gingivitis. Church & Dwight markets oral care products under brand names such as Arm & Hammer®, Aim®, Mentadent®, Close-Up®, and Pepsodent®. In addition to these comments containing its own suggestions, Church & Dwight endorses the comments submitted by CHPA and CTFA, which it participated in drafting.

Church & Dwight's comments center around a single issue: the draft guidance's attempt to establish certain standards for the design and evaluation of studies that go further than scientifically and clinically desirable and appropriate. When standards are set unnecessarily and inappropriately high, useful (i.e., effective) products whose benefits exceed their risks cannot come to market (or continue in the market), competition suffers, and consumers lose choices they could and should have had available to them.

FDA's approval of an NDA for a drug signifies its conclusion that the drug's benefits exceed its risk. In assessing whether a drug provides benefit, i.e., whether it is effective, FDA considers not only whether a drug has been shown to provide a statistically significant improvement over an appropriate comparator, but also whether the improvement is clinically meaningful. What kinds and degrees of benefit are clinically meaningful depend on the clinical

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context in which the drug will be used, the nature of the disease the drug is intended to treat or prevent, the safety of the drug under consideration, and other factors.

With respect to gingivitis, there is general agreement that gingivitis should be prevented or treated not only for its own sake but also to reduce the risk of progression to periodontitis. Report of the Dental Plaque Subcommittee, 68 Fed. Reg. 32232, 32237 (May 29, 2003). See, e.g., Loe et al., The clinical course of chronic periodontitis, IV, Gingival inflammation as a risk factor in tooth mortality, 31 J.Clin. Periodontol. 1122 (2004) (gingival inflammation is a risk factor for future tooth loss; the lower the amount of gingivitis, the lower the risk of tooth loss). Any reduction in gingival inflammation, i.e., gingivitis, is likely therefore to reduce the risk of periodontitis and associated tooth loss, and even a small reduction in the risk of periodontitis and associated tooth loss is beneficial, i.e., clinically meaningful.

But the draft guidance states that FDA will consider a gingivitis product to have shown “clinically meaningful” effects only if certain numerical criteria are met. The draft does not provide any reasons for its choice, nor discuss the factors that were evaluated and considered in arriving at the numerical criteria chosen. Instead, the draft guidance merely says it “concurs with the consensus of the expert dental community regarding therapeutically significant improvements in . . . gingivitis,” citing Imrey et al. FDA fails to recognize, however, that the ADA Task Force was explicitly making a recommendation not for criteria to be adopted by FDA, but for how the ADA should administer its acceptance program, i.e., the standards for the ADA’s decisions to endorse products by means of its seal. Unlike the ADA, FDA is not free to set the standards as high as it wishes as a matter of choice, but must instead consider how its scientific and clinical decision is fit within statutory and regulatory criteria. With a disease such as gingivitis, a reduction of 10% or even 5% may well be beneficial, i.e., clinically meaningful, and FDA would be doing a disservice to consumers by in effect ruling out products that can

provide such benefits. Moreover, the Task Force did not say that anything less than the numerical criteria it set would not be clinically meaningful. Rather, it expressed concern about only one issue – that it is possible, by means of conducting a very large study, to make very small differences statistically significant, even though they may not be clinically meaningful. That problem is well-recognized at FDA, and is in fact dealt with by the agency's requiring that an effect size be clinically meaningful as well as statistically significant. It is not appropriate for FDA to decide in advance that it will not even consider the possibility that a benefit is clinically meaningful because the size of the benefit is smaller than the ADA would award its seal to.¹

Another aspect of the problem lies in the draft guidance's proposal that studies to demonstrate efficacy in gingivitis be at least 6 months in duration. To date, products that have been shown to be effective for gingivitis have taken a considerable time – around 6 months – to demonstrate an effect. But there is no reason to study a product for six months if it is capable of demonstrating and does demonstrate efficacy in less time, e.g., 2 months. Requiring six month trials for products whose effects are manifest much earlier is a disincentive to innovation in this area.²

It is also important to consider effect size and duration of trials together. If the draft guidance is adopted as is, FDA will have expressed its preference for products that reduce gingivitis by about 20% compared to placebo, even if it takes six months to do so. But consumers might well prefer, and be meaningfully benefited by, a product that reduces gingivitis by 10% in 3 months, or a product that reduces gingivitis 5% in 1 month.

One other point deserves consideration, and that is the draft guidance's choice of endpoints for clinical trials of gingivitis agents. The draft guidance correctly notes that

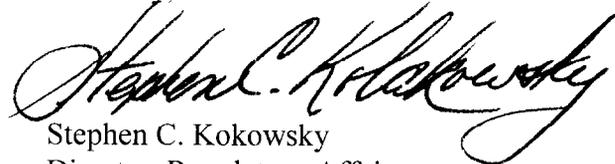
1 This is especially so when the ingredient that produces the benefit is very safe and has been widely and safely used in oral care.

2 In some cases, where the ingredient of interest is a new chemical entity or has not been used in regular oral care for gingivitis or any other indication, longer exposure may be important from a safety standpoint. But if the ingredient in question has been safely used in regular (chronic) oral care, additional safety data may not be necessary

“[b]leeding on probing is a cardinal sign of gingivitis.” But it then unaccountably (and with no explanation) limits the use of bleeding on probing to secondary status, and says it is not sufficient as a stand-alone primary outcome variable. We suggest the agency reconsider, and recognize bleeding on probing as an appropriate primary endpoint in gingivitis studies.

Thank you for considering Church & Dwight’s comments.

Sincerely,



Stephen C. Kokowsky
Director, Regulatory Affairs
Law Department

REF: Loe et al., The clinical course of chronic periodontitis, IV, Gingival inflammation as a risk factor in tooth mortality, 31 J.Clin. Periodontol. 1122 (2004)