



University at Buffalo
The State University of New York

Department of Oral Biology
School of Dental Medicine
Faculty of Health Sciences

October 19, 2005

Division of Documents Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

To whom it may concern,

We appreciate the opportunity to provide comment to "Guidance for Industry - Gingivitis: development and evaluation of Drugs for treatment or prevention", U. S. Department of Health and Human Services Food and Drug Administration, Center for Drug Evaluation and Research (CDER), June 2005, Clinical Medical.

Our concerns about the draft document center on the outcome measures used for anti-gingivitis products and clinical significance. We propose that standardized bleeding on probing be included as one of the possible primary outcome variables for use by clinical scientists in evaluating drugs for the prevention and treatment of gingivitis. We feel that it is sufficient as a primary outcome variable because:

1. it is an objective measure of gingival inflammation
2. it is a reliable and verifiable outcome measure (Marks, RG 1993; McClanahan, SF 2001)
3. it is highly correlated with histological changes of gingivitis (Caton, J 1988; Caton, J 1992; Caton, J 1988; Caton, JG 1985)
4. it is readily interpretable in terms of clinical significance (Van Dyke, TE 2005)
5. it is highly correlated with gingival indices such as the GI (McClanahan, SF 2001)

Clinical trials evaluating anti-gingivitis products have historically run into the thorny issue of how to measure gingivitis. Clinical trials evaluating anti-gingivitis products have used either a gingival index and/or a bleeding index. Gingival indexes (Gingival index (LOE, H 1963), Modified gingival index (Lobene, RR 1986)) are a subjective categorical ordinal evaluation of the color and the shape of the marginal gingival tissue. The draft recommendations are based, in part, on Imrey et al. 1994; (Imrey, PB 1994); however, in that paper, considerable controversy was expressed about use of the gingival index and its clinical significance, because "judgments of appearance have less claim to objectivity than gingival bleeding assessments, and the clinical significance of improved appearance without reductions in bleeding seems unclear" (Imrey, PB 1994, page 303).

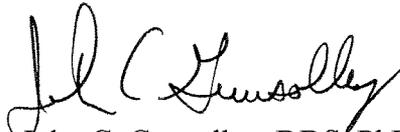
In conclusion, as clinical scientists, we would like the ability to use bleeding on probing as a primary outcome variable for studies evaluating drugs for the prevention or treatment of gingivitis. Bleeding on probing is objective, reliable, and verifiable by histology as a direct measure of gingivitis. Furthermore, bleeding on probing is meaningfully interpretable when assessing clinical significance. On all of these criteria, bleeding on probing meets or exceeds the gingival indices as a primary outcome variable. We also note that the guidance document should allow for the possibility or option of selecting future, improved measures of gingivitis for assessing new drugs.

We thank you for considering this request.

Sincerely,



Robert J. Genco, DDS, PhD
Distinguished Professor,
Oral Biology and Microbiology



John C. Gunsolley, DDS, PhD
Professor, Periodontology



Thomas E. Van Dyke, DDS, PhD
Professor, Periodontology
and Oral Biology

References

1. Marks, R G, Magnusson,I, Taylor,M, Clouser,B, Maruniak,J, and Clark,WB, Evaluation of reliability and reproducibility of dental indices 2. 1993; *J Clin.Periodontol.*; 20; 54 - 58.
2. McClanahan, S F, Bartizek,RD, and Biesbrock,AR, Identification and consequences of distinct Loe-Silness gingival index examiner styles for the clinical assessment of gingivitis. 2001; *J Periodontol.*; 72; 383 - 392.
3. Caton, J, Thilo,B, Polson,A, and Espeland,M, Cell populations associated with conversion from bleeding to nonbleeding gingiva 16. 1988; *J Periodontol.*; 59; 7 - 11.
4. Caton, J, Polson,A, Bouwsma,O, Blieden,T, Frantz,B, and Espeland,M, Associations between bleeding and visual signs of interdental gingival inflammation. 7. 1988; *J Periodontol.*; 59; 722 - 727.
5. Caton, J, Biological and measurement issues critical to design of gingivitis trials 10. 1992; *J Periodontal Res.*; 27; 364 - 368.
6. Caton, J G and Polson,AM, The interdental bleeding index: a simplified procedure for monitoring gingival health. 20. 1985; *Compend.Contin.Educ Dent.*; 6; 88, 90 - 88, 92.
7. Van Dyke, T E, The clinical significance of new therapies for the management of periodontal disease 21. 2005; *Journal of the international Academy of Periodontology*; 7; 191 - 196.
8. LOE, H and SILNESS,J, Periodontal disease in pregnancy. I Prevalence and Severity. 1963; *Acta Odontol.Scand.*; 21; 533 - 551.
9. Lobene, R R, Weatherford,T, Ross,NM, Lamm,RA, and Menaker,L, A modified gingival index for use in clinical trials. 1986; *Clin.Prev.Dent.*; 8; 3 - 6.
10. Imrey, P B, Chilton,NW, Pihlstrom,BL, Proskin,HM, Kingman,A, Listgarten,MA, Zimmerman,SO, Ciancio,SG, Cohen,ME, D'Agostino,RB, and ., Recommended revisions to American Dental Association guidelines for acceptance of chemotherapeutic products for gingivitis control. 2. 1994; *J Periodontal Res.*; 29; 299 - 304.