

INDIANA UNIVERSITY



November 23rd, 2005

0024 5 DEC -1 A9:47

SCHOOL OF DENTISTRY

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

**Re: Docket Number 2005D-0240 – Draft Guidance for Industry
Development and Evaluation of Drugs for Treatment or
Prevention
of Gingivitis.**

It appears that my electronic submission, sent on 10/27/05 was not received due to a technical complication.

I therefore submit in hard copy, attached.

Yours truly,

Michael J Kowolik

A handwritten signature in black ink, appearing to read "Michael J. Kowolik", with a horizontal line underneath.

DEPARTMENT OF
PERIODONTICS
AND
ALLIED DENTAL PROGRAMS

HOST DEFENSE LABORATORY

1121 West Michigan Street
Indianapolis, Indiana
46202-5186

Dr. Michael J. Kowolik
Email:
mkowolik@iupui.edu

Office:
317-278-0223
Laboratory:
317-278-0222
Fax:
317-274-1363

**Dr. Michael J. Kowolik
Professor and Director of Graduate Research
Dept. Periodontics & Allied Dental Programs
Indiana University School of Dentistry;
Dept. Public Health and Center for Bioethics
Indiana University School of Medicine
Tel: 317 278-0223
E-mail: mkowolik@iupui.edu**

*Located on the campus of
Indiana University
Purdue University
Indianapolis*

2005D-0240

C9

**Docket: 2005D-0240 - Draft Guidance for Industry -- Development and Evaluation of
Drugs for Treatment or Prevention of Gingivitis; Availability**

Temporary Comment Number: 27783-1 A9:47

Submitter: Dr. michael kowolik	Date: 10/27/05
Organization: Indiana University	
Category: Academia	
Issue Areas/Comments	
General	
"See Attachment"	
Attachments	
2005D-0240-T27783-Attach-1.txt	

Print - Print the comment
Exit - Leave the application

Comments re- Docket number 2005D-0240

“Guidance for Industry. Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention”

I wish to submit the following comments and observations regarding the above draft guidance document.

1. Specific comments:

Under item III F. Ethical Considerations of Conducting a Gingivitis Trial

It is agreed that the *Experimental Gingivitis Model* has specific relevance to only critical phases of product development. However, the ethical issues, if properly addressed, should not be a concern. There is no evidence, to my knowledge, that study participants have ever been harmed by inclusion in such studies that have been performed over the past 40 years. If there are concerns, they may be more related to the biological relevance of the model to the “natural” condition.

Under item VI B. Inclusion and Exclusion Criteria

The point concerning the inclusion of subjects “typical of those who might use the product” is well taken. For an OTC product, this would likely include minors, pregnant women, orthodontic patients etc.. Including such individuals in clinical trials can be problematic, since their clinical condition becomes a confounding factor, necessitating a huge increase in the size of the participant pool. It may be a useful recommendation to include such subjects as a sub-set, but not made mandatory unless the product indication is for that group.

On the topic of confounders, it is probably appropriate that in any equivalence study, female participants are asked to keep a diary record of their menstrual cycles.

Under item VII B. Gingival Index

This paragraph suggests that The GI, while universally popular, is equally “user-friendly”. That is true only in experienced hands and always with an

understanding of, and appreciation for, its limitations and pitfalls. Inter-examiner agreement, interpretation of the index and examiner styles of using the index have all plagued the interpretation of data from published studies.

I'm not so convinced that the literature supports the validity of using index teeth for gingivitis trials.

The last sentence refers to a completely unrelated clinical measure – that of periodontal pocket depth probing. If this is to be mentioned in this document, it requires elaboration. At least to stress again the importance of examiner skill, training, calibration and, most importantly, reproducibility.

Under item VII D. Bleeding on Probing

Some of the gingivitis indices, as stated, include a component for bleeding. This is important. Although it may be considered an arbitrary sign with respect to biological tissue changes, it is nevertheless what study participants and, ultimately, the public sees as the one indicator of their gum health. In that regard, I would contest that there are occasions on which bleeding on probing data might be the primary end point and visual signs of inflammation secondary.

Under item IX. Safety Considerations

In the final paragraph, it is good clinical practice that a “soft tissue oral examination” be undertaken at *every* visit in *every* trial. That is, this is not just *desirable* but *essential*.

Additional comment:

Under item II A, it is stated that this document *refers to plaque-induced gingival disease*, i.e. gingivitis. Gingivitis is a reversible, local tissue response and not an inflammatory entity such as rheumatoid arthritis, asthma or even periodontitis. By its clinical nature and definition, it is universal, varying only in severity, which also fluctuates under the influence of a myriad of factors. It is partly for this reason that there is so much difficulty in standardizing an assessment tool and an “intent to treat” criterion. I therefore welcome this document but equally urge that the FDA sees fit to further strengthen some of the recommendations after consideration of the above comments.

Respectfully submitted,

Dr. Michael J. Kowolik
Professor and Director of Graduate Research
Dept. Periodontics & Allied Dental Programs
Indiana University School of Dentistry;
Dept. Public Health and Center for Bioethics
Indiana University School of Medicine
Tel: 317 278-0223
E-mail: mkowolik@iupui.edu