

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[Docket No. 80N-0042]

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DMB

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Anticaries Drug Products for Over-the-Counter Human Use; Use of Intraoral Appliance Models for Compliance With Biological Testing Requirements; Request for Information and Comments

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is requesting information and comments on the use of intraoral appliance (IOA) models as a substitute for the animal caries reduction (“rat caries models”) biological test required by the monograph for over-the-counter (OTC) anticaries drug products to demonstrate the availability of fluoride in OTC dentifrice formulations. This notice is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Submit written or electronic comments by *[insert date 90 days after date of publication in the Federal Register]*.

ADDRESSES: Submit written comments to the Dockets Management Branch (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. Submit electronic comments to <http://www.fda.gov/dockets/ecomments>.

FOR FURTHER INFORMATION CONTACT: Robert L. Sherman, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:

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I. Background

The testing procedures for fluoride dentifrice drug products in 21 CFR 355.70 of the final monograph for OTC anticaries drug products (60 FR 52474, October 6, 1995), include both in vitro and biological testing to demonstrate the effectiveness of OTC anticaries dentifrices. The two in vitro tests (fluoride enamel uptake and enamel solubility reduction) demonstrate that fluoride is chemically available. The biological testing (animal caries reduction) assures that the fluoride is also bioavailable to alter tooth structure and make the tooth resistant to caries.

In the preamble to the final monograph for OTC anticaries drug products, FDA encouraged the development of additional testing procedures, such as remineralization tests. The agency noted that sufficient data were not available to correlate these tests specifically with clinical studies that demonstrate the effectiveness of fluoride dentifrices (60 FR 52474 at 52499). The agency stated that it would consider such tests as a substitute for the animal caries reduction test if adequate data were submitted demonstrating that an alternative testing procedure provides results of equivalent accuracy.

In 1996, FDA granted a petition (Refs. 1 and 2) that included the results of a study conducted in humans wearing an IOA with attached enamel chips as a substitute for the animal caries reduction test. Although the agency had initial concerns about the design and results of this IOA test, the data were considered sufficient to accept the test as an alternative to the animal caries model to demonstrate the effectiveness of the tested dentifrice formulation.

The petition also requested that the results of the IOA test be accepted as evidence of the effectiveness of the petitioner's other formulations. However, because these formulations contain different abrasives and flavorings, the agency determined that all other formulations must be tested individually (Ref. 2). The agency also recommended that protocols for any further IOA tests be submitted for review prior to conducting the tests.

IOA models employ small pieces of tooth enamel, mounted in the acrylic flanges of dentures worn by subjects that have been randomized to the various treatments to be investigated. The

enamel chips are examined for demineralization or remineralization using various test methods. Proponents of the IOA model argue that, when compared with the animal caries reduction test, the IOA test is more sensitive, reliable, and accurate, and that the testing does not require the sacrificing of animals.

Proponents add that a potential advantage of the IOA model is comparability to normal dentifrice use. In the animal caries reduction test, rats are superinfected with cariogenic bacteria and, unlike clinical subjects, swallow the fluoride toothpaste. Thus, it may be difficult to determine if the caries reduction is confounded by systemic absorption of fluoride. Further, the use of a removable appliance containing multiple enamel specimens offers a number of advantages. Most importantly, this method provides a sufficient number of specimens for several different analyses to be used: (1) Microradiography demonstrates the occurrence and extent of remineralization, (2) fluoride uptake measures in-situ bioavailability of fluoride, and (3) microhardness and acid-resistance testing measure the stability of remineralized enamel lesions. Multiple specimens also ensure that sufficient samples are available even if some are damaged during wearing or analysis.

In 1989, the Council on Dental Therapeutics (the Council) of the American Dental Association (ADA) accepted a new, modified fluoride dentifrice based largely upon data from IOA models, thus acknowledging that IOA models could be used as a potential indicator of clinical effectiveness. This marked an important departure from the Council's past practice of accepting modified anticaries agents only when conventional clinical trials had demonstrated a statistically significant benefit. Subsequently, the Council concluded that further consideration should be given to statistical issues related to IOA models and recommended that guidelines be developed concerning the validity and reliability of these models for use in approval of product claims (Ref. 3).

The animal caries reduction test has a long history of reliability in demonstrating the effectiveness of fluoride dentifrices. This test directly measures the effectiveness of a fluoride dentifrice in an animal model in vivo after limited brushing and gives a more complete assessment of tested formulations compared with the two in vitro tests (fluoride enamel uptake and enamel

solubility reduction). This test has been a requirement of the OTC anticaries final monograph since it was published in 1995. The anticaries final monograph provides general guidance on appropriate statistical analyses for the animal caries model.

In 1996, when FDA granted the petition to accept an IOA study as a substitute for the animal caries reduction test, the agency did not anticipate many similar requests. However, since that time, several citizen petitions (Refs. 4, 5, and 6) requested substitution of an IOA model for the animal caries test. Based on information in these petitions, the agency believes that a well-conducted IOA study can provide a measure of both remineralization and demineralization of tooth structure and potentially may provide results that, when compared to the animal caries model, are of equivalent accuracy.

The agency also received a citizen petition opposing these requests (Ref. 7). The petition presented two major criticisms of the IOA model: (1) It measures demineralization but not remineralization, and (2) it does not adequately mimic realistic caries challenges.

Thus, there is disagreement within the dental research community about whether IOA studies provide sufficient evidence of both demineralization and remineralization. There is also disagreement about whether the potential advantages of the IOA model, which uses human teeth, outweigh the predictability and the experience of the animal model.

II. The Current Request for Data and Information

Because of the lack of consensus within the dental community regarding the IOA test and the apparent increased interest among manufacturers to rely on this test in lieu of animal studies to demonstrate the effectiveness of new fluoride formulations, the agency has determined that it is appropriate to address these issues in a public forum where experts can debate the usefulness and acceptability of alternate biological testing methods such as the IOA model. The agency is publishing this notice to gather information concerning IOA models and whether and how they can be used in lieu of the animal caries models in meeting the biological testing requirements for OTC anticaries drug products. This information would include various study designs, the

parameters measured, methods for measuring these parameters, and the statistical methods employed to analyze the data. The agency would also like to have information concerning the statistical analyses that have been applied to the data generated by animal caries studies conducted to support monograph status for currently-marketed dentifrices.

In terms of study design, the agency is seeking information on both short-term and long-term IOA models. In the short-term study, the test product is used only once and the treatment phase lasts anywhere from 1 to 6 hours. In long-term studies, subjects wear the appliance for 2 to 8 weeks, using the test product several times a day. Because one of the criticisms of IOA models is their inability to measure remineralization, the agency seeks discussion regarding the ability of short-term and long-term studies to measure demineralization and remineralization.

Currently, the literature cites several ways of calculating the extent of mineralization or demineralization in these studies. Two common methods of measuring the percent mineral change in enamel are microradiographic analysis and microhardness testing. The agency requests detailed explanations of these methods, as well as others that are being proposed for this use. The agency also encourages discussion of the validity of substituting examination of mineral changes in the enamel chips in the IOA model for caries in the animal model. Further, the agency requests information on the validity of accelerating mineral changes in enamel both by soaking the chips in a sucrose solution and placing gauze over the chips to attract additional plaque.

Adequate demonstration of bioavailability in the biological testing models for fluoride dentifrices requires that the test product be significantly superior to the placebo, and noninferior to the reference standard performance. In the June 15, 1988, tentative final monograph for OTC anticaries drug products (53 FR 22430 at 22440), the agency discussed equivalence testing for the biological tests as follows: "The more general statement 'not significantly lower than the score for the reference formulation' allows the application of appropriate statistical criteria to laboratory data to demonstrate that fluoride dentifrices achieve scores in the biological tests that are not significantly lower than the scores for the reference formulations." The use of the appropriate

statistical analysis is further emphasized in the next paragraph of that section where it states: “Further, as stated in § 211.165(d) [21 CFR 211.165(d)], appropriate statistical quality control criteria must be used for drug products.”

Recent petitions requesting that the agency accept the IOA model in lieu of the animal caries reduction test have interpreted the phrase “not significantly lower than the scores for the reference formulation” as allowing the use of hypothesis testing as an acceptable statistical method. Although FDA considers computing p-values to be the correct method to test the hypothesis that a difference exists between the test product and placebo, the agency does not consider this method appropriate for demonstrating noninferiority of the test product to the reference standard. Failure to demonstrate a difference can result from several factors, including a small sample size, inappropriate adjustment, or poor study design. However, it is incorrect to infer from hypothesis testing that two products are equivalent or that one is not inferior, to the other. For the comparison between the test product and the reference standard, the agency believes that noninferiority testing, a subset of equivalence testing, is necessary.

The agency is seeking comment on statistical analyses that can be used to support the comparison between the test product and the reference standard. Because statistical testing for demonstrating superiority of a test dentifrice to a placebo dentifrice is generally straightforward, the agency is particularly interested in the statistical testing that would support either equivalence or noninferiority comparisons. Coupled with this, the agency is requesting information on whether the IOA models would require larger sample sizes than the animal caries models.

The agency anticipates that this information-gathering process will be followed by an advisory committee meeting at which the various models and the appropriate statistical analyses will be discussed.

III. Request for Comments

Interested persons may submit to the Dockets Management Branch (address above) written or electronic comments regarding this notice by *[insert date 90 days after date of publication]*

in the Federal Register]. Three copies of all written comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Dockets Management Branch between 9 a.m. and 4 p.m., Monday through Friday.

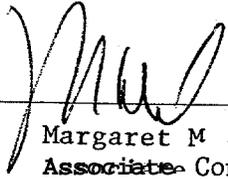
IV. References

The following references are on display in the Dockets Management Branch (address above) under Docket No. 80N-0042 and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. CP5.
 2. Comment No. LET35.
 3. Proskin, H. M., N. W. Chilton, and A. Kingman, "Interim Report of the Ad Hoc Committee for the Consideration of Statistical Concerns Related to the Use of Intra-oral Models in Submissions for Product Claims Approval to the American Dental Association," *Journal Of Dental Research*, 71:949-952, 1992.
 4. Comment No. CP7.
 5. Comment No. CP9.
 6. Comment No. AMD3:
 7. Comment No. CP8.
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Dated: 9/28/01
September 28, 2001.

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Margaret M. [unclear],
~~Associate~~ Commissioner for Policy:

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