Guidance for Industry

Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention

DRAFT GUIDANCE

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For questions regarding this draft document contact Fred Hyman, 301-827-2020.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

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Clinical Medical

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Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention

This draft guidance, when finalized, will represent the Food and Drug Administration's (FDA's) current thinking on this topic. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. You can use an alternative approach if the approach satisfies the requirements of the applicable statutes and regulations. If you want to discuss an alternative approach, contact the FDA staff responsible for implementing this guidance. If you cannot identify the appropriate FDA staff, call the appropriate number listed on the title page of this guidance.

I. INTRODUCTION

This guidance is intended to assist sponsors of new drug applications (NDAs) with the development of drug products that treat or help prevent gingivitis in adults and children. This document defines gingivitis and clarifies the distinction between gingivitis and periodontitis. It discusses general issues such as over-the-counter (OTC) versus prescription status and prevention versus treatment. The bulk of this guidance focuses on trial design issues and clinical assessments. The document concludes with an examination of product safety determinations.

This document does not contain discussion of the general issues of clinical trial design or statistical analysis. Those topics are addressed in the ICH guidance documents, *E8 General Considerations for Clinical Trials* and *E9 Statistical Principles for Clinical Trials* (ICH-E9).[2] This guidance focuses on specific trial design issues that are unique to the study of gingivitis.

FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are

[1] This guidance has been prepared by the Division of Dermatologic and Dental Products in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration (FDA).

[2] We update guidances periodically. To make sure you have the most recent version of a guidance, check the CDER guidance page at http://www.fda.gov/cder/guidance/index.htm.

cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

II. BACKGROUND

A. Definition of Gingivitis

Gingivitis is an inflammation of the soft tissue of the oral cavity that immediately surrounds each individual tooth. This soft tissue, known as the gingiva, consists of epithelial and connective tissues, which support the teeth in the bone of the mandible or maxilla. The other supporting structure that anchors the teeth is the periodontium, which consists of connective tissue attachments and alveolar bone. Whereas gingivitis is an inflammation confined to the gingival tissue, periodontitis affects the ligaments and alveolar bone that support the root of the tooth and provide its anchorage to the maxilla or mandible.

This guidance focuses on plaque-induced gingivitis, as it is the most common form of gingivitis and responds well to oral hygiene and antimicrobial products. Dental plaque is the aggregation of soft deposits that form the biofilm adhering to the teeth or other hard surfaces in the oral cavity, such as removable and fixed restorations. In addition to plaque, other causes of gingivitis include viral, fungal, or bacterial infection; endogenous sex steroid hormones; medication; systemic diseases; and malnutrition. Sponsors interested in developing products for gingivitis of nonplaque etiology can consult the Division of Dermatologic and Dental Drug Products for advice that is specific to that unique indication. In this guidance, the term *gingivitis* refers specifically to plaque-induced gingival disease unless otherwise noted.

B. Antigingivitis Rulemaking

During the past several decades, many products have entered the marketplace as OTC products that purport to treat or prevent gingivitis. As a result of the proliferation and promotion of those products, FDA convened a subcommittee of the Dental Products Panel (Subcommittee) in 1993 to evaluate OTC products that make gingivitis claims and that were in the marketplace without an NDA. The panel reviewed the data submitted for the antigingivitis products and reported its findings on the safety and effectiveness of OTC ingredients for the reduction or prevention of gingivitis.

On May 29, 2003, the Subcommittee's final report was published in the *Federal Register* (68 FR 32232) as an advance notice of proposed rulemaking (ANPRM). The ANPRM established conditions under which OTC drug products for the reduction or prevention of dental plaque and gingivitis would be generally recognized as safe and effective and not misbranded.
FDA is publishing this guidance document on the development of antigingivitis drug products to aid drug sponsors in conducting clinical trials either to submit additional information to the antigingivitis rulemaking, or to obtain approval for a new antigingivitis drug through the NDA process.

III. GENERAL CONSIDERATIONS

A. Prescription vs. Over-The-Counter Status of the Drug

One early consideration in drug development is whether the drug product is to be marketed as a prescription medication (including drugs available only to practitioners) or as an over-the-counter (OTC) preparation. An expert panel convened by FDA in 1991 determined that the general public is able to recognize and self-treat gingivitis. Drugs that the public can use appropriately in the absence of supervision by a physician, dentist, or other health care practitioner are marketed OTC.[3] OTC status is not appropriate for antigingivitis products that call for supervised use.

Unlike a prescription drug label, an OTC label should contain indications, directions for use, and warnings that are understood by the general public. Comprehension studies can demonstrate that consumers will be able to understand and follow labeled directions and warnings. Sponsors of OTC products should demonstrate that consumers can use these products safely since there will be no health professional monitoring for adverse events or symptoms of more serious conditions, such as periodontitis. Safety considerations for both prescription and OTC antigingivitis drugs will be discussed in detail in section IX of this document.

B. Prevention vs. Treatment Claim

Another consideration is whether the therapy is intended to prevent or to treat gingivitis. Many studies begin with subjects receiving a professional scaling and polishing that alone may restore gingival health. The endpoint then may be the reappearance of gingivitis after a set period of time. If the test group develops significantly less gingivitis than the placebo group in appropriately designed studies, it is reasonable to conclude that the drug has reduced the incidence of gingivitis. In the case of a chronic disease such as gingivitis, *prevention* is more explicitly stated as "reduces the incidence of disease" or "reduces the incidence of severe disease." Wording that conveys this message would vary, depending on whether the product is intended for prescription or OTC use. Wording for a prescription product could include scientific language such as "reduction of disease incidence." To convey this message on a level more appropriate for consumers of nonprescription drugs, the Subcommittee has recommended that OTC products carry the language "helps prevent gingivitis."

Subjects who already have measurable gingivitis before treatment may experience a significant reduction in the mean gingivitis score or in the number of gingivitis sites in the test group compared to placebo group (scoring systems are described in section VII of this document). This reduction would allow for a claim of "reduces the severity of gingivitis" or some other treatment claim as appropriate for prescription or OTC status.

[3] 21 U.S.C. 503(b)(1)(A) of the Federal Food, Drug, and Cosmetic Act.

C. Mechanism of Action

Understanding a drug's mechanism of action is desirable but not required for FDA approval for marketing. There is a safety concern in treating gingivitis without removing one well-established causal factor, plaque accumulation. Therefore, if the mechanism of action of the sponsor's drug were other than plaque reduction (e.g., anti-inflammatory), the sponsor would be asked to address the issue of masking underlying periodontitis before approval. Further discussion on this topic can be found in sections VII and IX of this document.

D. Dose-Response Relationship

We strongly encourage the sponsor to explore the dose-response relationship early in product development. It is always desirable to identify the lowest effective dose for a drug. In the case of topical antigingivitis products, not only should the lowest concentration of the drug be identified, but also both the lowest effective frequency of dosing and the shortest duration of therapy. As gingivitis is not a life-threatening disease and other treatments for gingivitis are available, an unfavorable adverse events profile for a new antigingivitis drug could jeopardize approval, depending on the severity and seriousness of the events. A lower dose of the drug might be effective and provide an appropriate safety profile.

E. Combination Products

Two or more drugs can be combined into a single dosage form when each component makes a contribution to the claimed effect or effects (21 CFR 300.50 and 330.10(a)(4)(iv)). To demonstrate the contribution of each component, we recommend that the combination product be shown to have a greater effect than either component separately in the same vehicle, if the product is for topical use. For example, if two antimicrobials are combined into one topical drug product for the treatment of gingivitis, the following arms should be included in the efficacy studies: vehicle, antibiotic A only in vehicle, antibiotic B only in vehicle, antibiotics A and B combined. To successfully demonstrate the efficacy of A and B together, the A+B arm should be significantly better at gingivitis reduction than both A alone and B alone.

F. Ethical Considerations of Conducting a Gingivitis Trial

It is important that study subjects not be exposed to permanent detrimental health outcomes as a result of their participation in a clinical trial, and that subjects understand the risks and benefits involved in their participation. As long as the group receiving the vehicle also receives standard oral care, there is no ethical concern because gingivitis is reversible. Gingivitis trials often begin with a professional oral hygiene appointment, which will benefit subjects in both the vehicle and test groups.

An example of a clinical trial with a potential ethical concern is a study of individuals with either severe gingivitis or gingivitis in conjunction with periodontitis. In these cases, a delay in

treatment may cause irreversible damage. To avoid this possibility, the sponsor may wish to employ an active control and test for equivalence or non-inferiority to the active control. Rather than statistical testing for superiority to a placebo, confidence interval testing for equivalence would be used. Refer to ICH-E9 for a discussion of the statistical considerations of this trial design. Also refer to subsection VIII.B of this document.

In the past, experimental gingivitis models have been used to accelerate the development of gingivitis to shorten the trial. Although this may be valuable during early phases of drug development to determine if the test product has the potential to be effective, the ethics of this approach raise concern. We recommend that sponsors carefully consider factors such as the health of the subjects, duration of the proposed trial, and possibility of irreversible damage. Also, these experimental gingivitis studies do not represent the natural history of gingivitis and may produce misleading results.

IV. NONCLINICAL CONSIDERATIONS

This section of the document concerns nonclinical development issues related to products that are intended for administration within the oral cavity for the treatment or prevention of gingivitis. These comments are intended to supplement the applicable FDA guidance documents that pertain to nonclinical development and should be considered within the context of those documents.

The safety assessment of antigingivitis products should include consideration of the potential to cause both local (inside the mouth or gastrointestinal tract) and systemic toxicity. Even if the product is not intended to be swallowed, the sponsor should assume that a portion of each dose will be swallowed, and many compounds are absorbed buccally or sublingually. Evaluation of the systemic toxicology of compounds that are proposed for the treatment or prevention of gingivitis should follow the same precepts that apply to development of the nonclinical safety database associated with most other systemically administered compounds. The ICH guidance, *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*,[4] provides an overview of the general types of nonclinical data that may be important to support various stages of clinical development and marketing of drug products. It also gives information about the recommended durations of the exposures of the animals to the test materials and the time at which certain nonclinical data should be available relative to clinical development. For details concerning general toxicological issues, refer to the appropriate CDER guidance documents.[5]

Systemic toxicity issues that concern these products are usually best assessed through toxicology studies of appropriate duration and design in which the drug substance (not necessarily the drug product) is administered orally (usually by gavage, but in some instances in the diet or drinking water). The studies should include thorough clinical pathology (i.e., clinical chemistry,

[4]Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.
[5]Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

hematology, and urinalysis), histopathological examination of a full range of tissues, and toxicokinetic analysis. The gastrointestinal tract is an area of particular concern since it may be exposed to the materials in relatively undiluted form. Toxicokinetic data from these studies should be compared to pharmacokinetic data obtained in suitable clinical studies conducted with the drug product to ensure that systemic exposure in the nonclinical studies was adequate to qualify the clinical exposure. If acute studies are performed, we recommend that the studies include animals that are sacrificed at an early time point (e.g., 24 hours post-treatment), since mucosal lesions heal rapidly. Development of sustained-release products should include studies in which the intact product is administered by gavage to a suitable species, with emphasis on determining whether or not the product causes erosions or ulcers.

For products that are intended for direct administration within the mouth, such as mouthwashes, dentifrices, and intraoral sustained-release products, we recommend that sponsors consider the products' potential to induce irritation or erosion of the oral tissues. The most appropriate means of addressing this issue depends on the circumstances associated with a particular product and clinical proposal; data from an oral irritation study conducted in animals may be unnecessary. For example, if a product is very similar to a formulation that has been studied previously (in animals or humans) without excessive local irritation, then additional oral irritation data may not be warranted. Another factor that should be considered when assessing the importance of oral irritation data in support of a given clinical proposal is the design of the proposed clinical study. That is, what steps would be taken to detect oral irritation at an early stage, and what measures would be taken if irritation is observed? For example, the clinical protocol may call for a qualified individual to examine the oral cavity at appropriate time points (e.g., following 1, 3, 7, and 14 days of treatment), with termination of dosing if signs of irritation are evident. In this instance, carefully collected data from patients makes an oral irritation study in animals less relevant, compared to a trial with less frequent or less comprehensive oral examinations. These matters should be considered on a case-by-case basis, and the review division can be contacted for specific guidance.

If it is deemed important to evaluate a product for potential to induce oral irritation in an animal model, then we suggest that the following points be considered during the design of an oral irritation study:

- **Test material.** The material that is tested should be the same formulation (including inactive ingredients) that is proposed for use in humans. Sponsors should recognize that inactive ingredients (e.g., alcohol, flavoring agents, surfactants) in drug products are often irritating to the oral tissues.

- **Animals.** Rats or hamsters are generally used, although other species, such as dogs, may be appropriate in certain instances. It is recommended that animals of both sexes be studied.

- **Abrasion of the mucosa.** One of the goals of an oral irritation study should be to assess the product for potential to delay healing of lesions within the oral cavity.

This goal can be accomplished by comparing the rates at which mechanically induced oral lesions heal in treated and control animals. Therefore, a portion of the oral mucosa of each animal should be abraded shortly before the first application of the test and control materials. The buccal mucosa should be abraded on only one side of the mouth, permitting examination of both intact and abraded mucosa in each animal. Abrasion can be accomplished with a variety of instruments (e.g., file, brush, needle). It is important that the location, size, and depth of the abrasions be as uniform as possible within a study. The abrasion should be sufficiently severe that a lesion extending into the sub-epithelial connective tissue is observable in tissue sections from animals sacrificed 24 (or more) hours after treatment. Ideally, the abrasion procedure, including the time course of the healing process, should be histologically characterized before initiation of a definitive oral irritation study.

- **Method of application.** The test material should be applied to the oral tissues in a manner that is reproducible in terms of (1) the quantity of test material that is applied to the oral cavity, (2) the oral tissues to which the test material is directly applied, and (3) the amount of application-induced abrasion of the oral tissues. The duration and pattern of each application should be consistent. The test material is usually applied with a cotton swab. In general, the animals should not be anesthetized during treatment, since many anesthetics impair salivation. Placement of the test material within the cheek pouch of a hamster is not particularly recommended, because the amount of time that the test material is retained within the pouch may vary substantially among animals (or between control and active materials). An exception to this statement pertains to situations in which a solid dosage form (e.g., an osmotic tablet) should be retained in the mouth for a substantial period, in which case it may be appropriate to place the test material in the cheek pouch of an anesthetized hamster and suture the pouch partially closed to prevent expulsion.

- **Dosage level.** A dosage of 1 milliliter or 1 gram of test or control material per kilogram of body weight per application is generally used, although different dosage volumes may be deemed appropriate on the basis of toxicity or the clinical dosage. If it is considered important to examine the effect of a range of exposure levels (i.e., evaluate the dose-response relationship associated with irritation of the oral tissues), the intensity or magnitude of the daily exposure to the test materials should be regulated through modulation of the dosing frequency. For example, a study might include a group of animals that were treated once daily, a second group that were treated twice daily, and a third group that were treated four times daily. The exposure level should not be modulated through variation of the quantity of material administered per application, since excess test material is usually swallowed or expelled without genuinely increased exposure of the oral cavity to the material.

- **Dosing frequency.** The number of daily applications should at least equal, and preferably exceed, the maximum anticipated clinical dosing frequency for the product

(although generally the maximum feasible number of applications per day in an animal study is four, at 2-hour intervals).

- **Duration of application.** We recommend that the animals be treated for 28 consecutive days; a study of this duration should adequately support an NDA for a product that is proposed for chronic use (with respect to oral irritation), since local effects will be apparent within that time frame.

- **Controls.** The study should include a negative control group consisting of animals treated with room temperature distilled water or 0.9 percent sodium chloride (NaCl). The vehicle of the drug product should *not* be used as a negative control article, as some inactive ingredients may be irritating.

- **Sacrifice schedule.** We recommend that the oral tissues be histopathologically evaluated at selected intervals during the study following interim sacrifices. For example, in a study in which animals are to be treated for 28 days, with the day on which abrasion and the first treatments are performed being designated day 1, animals might be sacrificed on days 2, 5, 29, and 43. The sacrifice on day 2 (approximately 24 hours after the abrasion of the mucosa) would permit assessment of the adequacy and uniformity of the abrasion technique, and might involve only a small number of randomly selected negative-control animals (e.g., three animals per sex). We recommend that an interim sacrifice of animals in each treatment group be conducted at a time point when the abraded mucosa in the negative control animals is partially (but not completely) healed. The purpose of this interim sacrifice is to provide information concerning the potential of the test material to delay healing of lesions of the oral mucosa, which could be accomplished through comparison of the abraded areas from test and control animals. Although it is suggested in this document that sacrifice on day 5 *may* be appropriate for assessment of effect on healing, the optimum time point will depend on various factors, including the nature of the initial abrasion. The time point that is selected should be based on data from previous studies that used an identical abrasion technique and evaluated the time course of healing of the lesion. Animals sacrificed on day 43 (14-day recovery group) could provide information about the reversibility of any lesions observed in animals sacrificed on day 29.

- **Number of animals.** A typical study design might involve 18 animals per sex in the negative control group and 15 animals per sex in each group that is to be treated with a test material. Such a study could involve sacrifice of 3 negative-control animals per sex 24 hours following abrasion (for assessment of the abrasion technique) and 5 animals per sex from each group on the date of the interim sacrifice (see the previous bulleted item above) and on days 29 and 43.

- **Parameters to be evaluated.** The oral cavity of each animal should be visually inspected at least once daily, including evaluation of the colors of the oral tissues

(including the teeth), signs of edema, erythema, sloughing, bleeding, or ulceration, and the presence of dryness, roughness, cracking, or bleeding of the lips. Terminal studies should include gross examination of the oral cavity, esophagus, stomach, small and large intestine, and any apparent lesions, and histopathology of the oral cavity and adjacent structures, including the labial junctions, the buccal and gingival tissues (including the area that was abraded), the tongue, the palate (hard and soft), the parotid salivary gland, the submandibular lymph nodes, the nasopharynx and nasal passages, the larynx, the esophagus, the stomach, and any tissues that appear abnormal during gross examination. Particular emphasis should be placed on the integrity and thickness of the epithelial barriers, signs of hyperplasia or keratinization, examination of the area that was abraded for signs of delayed healing (relative to the negative control animals), and examination of the soft tissues for infiltration of inflammatory cells and/or edema.

V. CLINICAL PROTOCOL ISSUES AND ELEMENTS

A. Study Design

Parallel group designs are commonly employed and generally recommended. We advise sponsors to exercise caution with the use of crossover and split-mouth designs, which rarely offer any advantage. A split-mouth design, in which one side of the mouth is untreated and is used as a control and the other side treated, may be difficult to execute. Test agent from the treated side may contaminate the untreated side and compromise the results. In a crossover design, a sufficient wash-out period is important to eliminate any residual effects from prior treatments.

B. Randomization

A clear description of the method by which subjects are randomized to treatment groups, as well as identification of stratification variables and blocking factors, will demonstrate whether group allocation is unbiased.

Age, sex, and disease severity are important factors in consideration of the adequacy of randomization. Proper randomization of subjects will create balanced groups with respect to demographic and baseline characteristics. Enrollment of a diverse population may allow for detection of racial, sex, or age differences in response to treatment. For further information on this topic, refer to section VI.C of this document as well as the following guidance documents:[6]

- *Study of Drugs Likely to be Used in the Elderly*
- ICH *E11 Clinical Investigation of Medicinal Products in the Pediatric Population*

[6]Available on the Internet at htttp://www.fda.gov/cder/guidance/index.htm.

- ICH *E-7 Studies in Support of Special Populations: Geriatric*

In the case of an important potential confounder, such as baseline gingivitis or smoking, it may be prudent to stratify the groups by this factor before randomization. In some cases, adjustments for baseline characteristics may be accomplished statistically after the trial, to correct for differences. If that is anticipated, characteristics should be prespecified in the statistical plan. For multicenter trials, randomization of subjects within each center will help to ensure that none of the centers is unbalanced in its assignment of subjects to groups. More detailed information on randomization can be found in the ICH guidances, *E9 Statistical Principles for Clinical Trials* and *E10 Choice of Control Group and Related Issues in Clinical Trials*.[7]

C. Blinding

We recommend a double-blinded trial design whenever possible. Should blinding be compromised, the resultant bias may potentially invalidate the results. In the case of a topical product, differences in packaging or discernable characteristics, such as appearance (including viscosity, color, and opacity), smell, taste, or texture, may compromise blinding.

D. Length of Trial

Trial length may affect the demonstration of both safety and efficacy. In terms of efficacy, sponsors should allow sufficient time to demonstrate a significant effect, should it exist, and in the case of a chronic-use product, to demonstrate that the effect is not transient. A description of what constitutes a significant effect is discussed in detail in section VIII of this document. Data from Phase 2 dose-ranging studies can guide sponsors in determination of trial length. The review division generally recommends studies of 6 months duration or longer. In addition, 6 months is the typical interval between routine dental visits and therefore corresponds to clinical practice. In terms of safety, the ICH guidance, *E1A The Extent of Population Exposure Required to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-Life-Threatening Conditions* (ICH-E1A),[8] suggests the number of subjects that should be exposed to the drug for 6 months or longer to adequately detect uncommon adverse events. OTC drugs may call for additional safety testing because of their wider use and lack of professional oversight.

E. Standard of Care

During a chronic study (6 months or longer), subjects should receive the standard of care for gingivitis. This care consists of regular brushing and use of dental floss between professional dental visits to maintain oral health and reduce the incidence and severity of gingivitis. Subjects should be instructed to continue these measures throughout the trial. As would be typical of a dental visit, hygiene instruction should be provided at the baseline visit. In addition, unless the

[7] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.
[8] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

trial is specifically designed to measure gingivitis reduction in individuals who do not receive regular dental care, a professional scaling and prophylaxis should be performed at baseline.

F. Placebo or Active Control Formulation

To produce valid conclusions about the results of a clinical trial, we prefer that the trial be designed so that the test and placebo (or active control) groups differ only in the presence or absence of the active ingredient or ingredients. Differences in inactive ingredients, such as abrasives, sweeteners, and even dyes (which may have antimicrobial properties), may confound the data.

G. Use of a No-treatment Group

Use of a no-treatment arm in addition to the placebo and the test product groups allows for not only comparing the gingivitis effects between the test product and placebo, but also for examining any therapeutic effect of the vehicle. Subjects in this no-treatment arm would be instructed only to maintain their normal home oral hygiene regimen. This study is ethical only for study of gingivitis that is not severe or gingivitis not accompanied by periodontitis. For further discussion on ethical concerns, refer to subsection III.F of this document.

VI. CONSIDERATIONS FOR SUBJECT RECRUITMENT

A. Sample Size

This subsection gives a brief discussion of some points the sponsor should consider regarding sample size. For further discussion on sample size, refer to the ICH guidance, *E9 Statistical Principles for Clinical Trials* (ICH-E9). Note that the power calculations used to choose a sample size are affected by the duration of the gingivitis trial. Choosing a time period shorter than the recommended 6 months allows less time for a significant difference between the treatment and nontreatment groups to develop and may call for a larger sample size. Also, note that ICH-E9 focuses on the sample size a sponsor would choose to demonstrate efficacy. As discussed in section IX of this document, the number of subjects that adequately demonstrate safety may be greater than the number that would demonstrate efficacy.

B. Inclusion and Exclusion Criteria

Carefully chosen inclusion and exclusion criteria will allow for enrollment of the appropriate population to test the product for the target group. Of special consideration is the degree of gingivitis appropriate for enrollment, which will depend on the intended claim for the drug product and whether it would be marketed by prescription or OTC. A product intended to be marketed only with a prescription from a dentist would be appropriate for a population with gingivitis of a severity that would warrant a dentist's intervention. Testing for that product would focus on enrollment of subjects with this same level of severity. A product intended to be marketed OTC would be labeled for patients with a lower level of severity that may range from

very mild to moderate disease. We recommend that a product intended to be marketed OTC be studied in a population which includes a full range of gingivitis within the indication for nonprescription users to reflect the population that will ultimately use the product.

Another consideration in OTC drug testing is the influence of confounding factors such as pregnancy, diabetes, smoking, and presence of orthodontic brackets or removable prosthetic appliances. Many sponsors prefer to exclude individuals with these conditions to eliminate the difficulty of recording accurate measurements on them and the confounding effect of their conditions on gingivitis. Excluding these individuals in a trial for an OTC product is discouraged because those individuals will have access to the product in the marketplace, and the study population should reflect the population that will ultimately use the product. There is somewhat more flexibility in the trial of a drug that will be limited by prescription status, as the prescription label can convey information to the health professional, who can then make a decision about prescribing. Even in studies for prescription products, a rationale should be provided for excluding some patients (e.g., known lack of efficacy, safety issues, and ethical issues).

1. Recommended Inclusion Criteria

Basic conditions that are common to all gingivitis trials would include recruitment of subjects who are in good general health and who have the ability to provide written informed consent. Below are examples of possible inclusion criteria for gingivitis trials:

- a specified minimum number of teeth present
- a qualifying baseline plaque index
- a qualifying baseline gingival index (GI)
- presence of bleeding site or sites upon probing

The plaque and gingival indices are discussed in section VII of this document.

2. Recommended Exclusion Criteria

General exclusion criteria for clinical trials can include known hypersensitivity to any component of the test product or a closely related product, concomitant participation in any other clinical study, or a positive urine test for drugs of abuse. Because residence in the same household as a subject already enrolled in the study may create blinding and compliance issues, this also may warrant exclusion from the trial.

For typical gingivitis trials, we do not recommend exclusion of subjects based on age, race, or sex. Representation of special populations is expected (see section VI.C of this document entitled *Special Populations*). There may be cases where pregnant subjects would be excluded because of safety considerations or concerns about the confounding effect of pregnancy on gingivitis; however, we discourage automatic exclusion because of pregnancy. Other exclusions would depend on the drug product (e.g., gastrointestinal bleeding for an antigingivitis drug that is

a nonsteroidal anti-inflammatory). As was discussed earlier in this section of the document, trials for OTC products might have fewer exclusion criteria because it is important that the products be tested in a wider range of subjects. Below are examples of typical exclusion criteria for gingivitis trials:

- Gross oral pathology, including widespread caries or chronic neglect, extensive restoration, pre-existing gross plaque or calculus, or soft or hard tissue tumor of the oral cavity.

- Chronic disease with concomitant oral manifestations.

- Medical conditions or significant laboratory abnormalities that the investigator considers significant and that may compromise the subject's safety.

- Medical conditions that may affect the evaluability of the study results, such as clinically significant organic disease, including heart murmur, history of rheumatic fever, or valvular disease.

- Treatment with antibiotics within the 1-month period before the screening examination, or having a condition that is likely to call for antibiotic treatment over the course of the trial. This list includes cardiac conditions requiring antibiotic prophylaxis, such as heart murmurs, pacemakers, or prosthetic heart valves, as well as non-oral prosthetic implants.

- Orthodontic appliances or removable partial dentures.

- Periodontitis as indicated by clinical attachment loss, radiographic alveolar bone loss, or periodontal pockets greater than 5 millimeters.

- Concomitant pharmacotherapy with drugs that may interact with test drug.

- Chronic treatment (2 weeks or more) with any medication known to affect periodontal status (including phenytoin, calcium antagonists, cyclosporin, coumarin, nonsteroidal anti-inflammatory drugs, and aspirin) within 1 month of the screening examination. All other medications for chronic medical conditions have been initiated at least 3 months before enrollment.

- History of early-onset periodontitis or acute necrotizing ulcerative gingivitis.

- Concomitant endodontic or periodontal therapy other than prophylaxis in the last 6 months.

534
535 **C. Special Populations**
536
537 It is important to examine the effects of sex, race, and age in the clinical trials by enrolling
538 sufficient numbers of subjects with a diverse demographic background. Although there is no
539 evidence to demonstrate that individuals of certain races are predisposed to gingivitis, factors
540 such as access to health care, nutritional status, and socioeconomic status may be confounding
541 factors that affect the validity of results obtained through uneven distribution. Age and sex
542 may affect gingivitis both physiologically and psychosocially. For example, frequency of
543 professional visits is greater in adult women than men, and oral hygiene habits are highly
544 inconsistent in children and adolescents. In addition, during puberty and pregnancy, hormone-
545 associated gingivitis becomes a confounder. Furthermore — depending on the proposed therapy
546 — drug absorption, distribution, metabolism, and excretion may be different in different races or
547 between men and women, or between children and adults.
548
549 Smoking and diabetes are both significant risk factors for gingivitis, and it is important that they
550 be considered in the clinical trial design. Excluding subjects with these conditions in Phase 3
551 studies based on lack of efficacy in these groups in Phase 2 is a possibility. The labeling may
552 then reflect that these groups were not studied in Phase 3 after negative results in Phase 2.
553 Stratifying by these factors is preferred because this allows study of these groups but protects
554 against bias. Another possibility is to include all subjects but enroll a sufficient number so that
555 they can be analyzed separately. If smokers and diabetics respond more slowly or to a lesser
556 extent than others in the trial, this would be valuable clinical information for labeling.
557
558 **D. Pediatric Populations**

559 Gingivitis can be found in all age groups. In a comprehensive 1989 national survey conducted by
560 the National Institute of Dental and Craniofacial Research, 47 percent of adult males and 39
561 percent of females exhibited at least one gingivitis site as demonstrated by bleeding on probing.
562 Like adults, children are susceptible to plaque-induced gingivitis. The prevalence of gingivitis
563 among school-aged children in the United States has ranged from 40 to 60 percent in national
564 surveys. Adolescents have the highest prevalence and greatest severity of gingivitis of any age
565 group.
566
567 Conducting clinical trials in children is challenging. Nonetheless, § 201.57(f)(9) (21 CFR
568 201.57(f)(9)) charges the sponsor with the provision of safety and efficacy information on
569 children before drug approval. The pediatric plan can be tailored to the individual drug in
570 question. If safety and/or efficacy in children cannot be extrapolated from studies in adults, it
571 should be specifically demonstrated through enrollment of children in the same trials as adults or
572 by conducting separate trials in children.
573
574 **E. Geriatric Populations**
575

A *Geriatric Use* section in labeling has been a requirement for approval since August 27, 1997 (21 CFR 201.57(10)(ii)). Gingivitis affects individuals older than age 65 in significant numbers, and these individuals may respond differently to the drug product than younger adults. We encourage sponsors to (1) study a sufficient number of geriatric subjects to uncover any age-related differences in safety or efficacy, and (2) describe these differences in the drug labeling. For further information, including recommended labeling language, refer to § 201.57(f)(10) entitled *Geriatrics Use*.

VII. ASSESSMENT OF GINGIVITIS

We recommend that primary and secondary endpoints be clearly identified before initiation of the trial and prospectively described in the protocol, along with the statistical analysis methodology. The most common primary endpoint is a change in the gingival index (GI), which is a categorical scale to which values are assigned for degrees of gingivitis. Since the most common form of gingivitis is plaque-induced, a co-primary endpoint for most antigingivitis drugs is plaque index (PI) reduction. A common secondary outcome variable is the bleeding index. These indexes are discussed in greater detail later in this section of the document, and the condition under which a PI can be used as a secondary endpoint is discussed in section VIII of this document.

A. Calibrating Investigator Skills

Proper staff training helps to ensure consistency in recording of data and use of instruments. Reducing examiner variability is beneficial, as a decrease in measurement error can reduce the sample size that would be appropriate for a clinical trial. To the greatest extent possible, we suggest that examiner skills be calibrated to consistently perform reliable and accurate readings. As most trials employ several examiners, inter-observer variability may be an issue. With proper randomization and blinding, individuals in the test group and those in the placebo group will be fairly evenly divided between examiners. Scheduling a reasonable number of examinations per session with adequate rest periods will help maintain examiner efficiency. It has been noted in clinical trials that examiners trained at the beginning of an investigation adopt this new training initially but revert to their original methods by the end of the trial. Therefore, we recommend that training programs use reinforcement lessons throughout the duration of the study.

B. Gingival Index

Several gingival indexes have been used over the years. One gingival index that was developed in 1963 and is widely used today is the Loe and Silness Gingival Index. This index has proved useful in controlled clinical trials because it (1) is fairly sensitive to small changes, (2) is simple to administer, and (3) permits calibration of the examiners to minimize inter- and intra-examiner error. In this index, the gingival tissues surrounding each selected tooth are divided into four areas for scoring: distofacial papilla, facial margin, mesiofacial papilla, and the entire lingual margin. Each of these units is scored for gingivitis according to criteria that categorize each surface as 0 for normal gingiva, 1 for mild inflammation, 2 for moderate inflammation, or 3 for

severe inflammation. Literature is available that describes the details of this index, including those characteristics that accompany each score. The scores from the four gingival units are averaged to obtain a score for each tooth, and these scores are combined and averaged to determine a score for each individual. The index is sometimes scored on the entire dentition; literature is also available that supports using certain *index* teeth that are representative of the entire dentition. In this index, a periodontal probe is used to determine the bleeding tendency of the tissues. It is important that standardized pressure be exerted during the probing. Automated periodontal probes may improve the accuracy and precision of probing depth measurements.

C. Plaque Index

When plaque accumulates along the tooth surface, the gingiva responds to the bacterial insult with varying degrees of redness, edema, and bleeding. Regular removal of plaque through good oral hygiene maintains healthy gingiva and reduces the incidence of associated gingivitis.

It is the Agency's current thinking that antigingivitis drugs using a mechanism other than plaque reduction, such as anti-inflammation, could be approved as prescription drugs. However, without adequate professional oversight, chronic use of an anti-inflammatory drug that does not concomitantly reduce plaque has the potential to mask underlying infection. Therefore, antigingivitis drugs intended for OTC use would assign PI outcome as a co-primary, rather than a secondary, endpoint. This subject is discussed further in section VIII of this document.

Most trials employ a method of supragingival, rather than subgingival, plaque measurement because of the difficulties in accurately observing subgingival plaque. The Turesky modification of the Quigley and Hein Plaque Index has received considerable use in measuring plaque changes during clinical trials. In this index, plaque is identified using a disclosing solution and scored using a 0 to 5 scale in which a score of 0 corresponds to no plaque present, and a score of 5 designates plaque covering more than two-thirds of the tooth surface. Each tooth receives mesial, middle, and distal scores for both the facial and lingual surfaces. An individual's score is derived by adding the scores at each site and dividing by the number of sites evaluated. The Loe and Silness Plaque Index is also used in clinical trials. It employs a scoring scale from 0 to 3 and evaluates four sites on each tooth.

Sampled plaque is often weighed, either dry or wet. Note, however, that neither the PI nor quantification of dry or wet plaque weight correlates strongly with gingivitis. No single measurement can relate the various aspects of plaque accumulation, such as surface area of plaque, mass of the plaque, density of plaque, bacterial composition, and location on the tooth. The effect of plaque is most likely a combination of all these factors, which have not been captured in a single index or measurement.

D. Bleeding on Probing

Bleeding on probing is a cardinal sign of gingivitis. Some GI's include an assessment of bleeding. For those that do not, a categorical evaluation (yes or no) of bleeding on probing can

add valuable information. Bleeding can be an appropriate secondary outcome variable. It would not be sufficient as a stand-alone primary outcome variable.

E. Calculus Formation

The FDA views calculus reduction as a cosmetic claim rather than a drug indication; cosmetic claims are not included in prescription labeling. Certain topical dental drugs increase calculus formation, which is considered an adverse event. We encourage the sponsor of an antigingivitis product to include calculus examinations in both the baseline and the end-of-the-study evaluations. The labeling for a product that increases calculus formation would reflect this risk.

F. Staining Index

Improvement of extrinsic staining of teeth, like calculus reduction, is regarded as a cosmetic claim. Also, like calculus formulation, some antigingivitis products are known to result in increased staining on teeth. Increased staining is an adverse event that should be communicated to consumers. For products thought to cause staining, it is important to obtain measurements on a staining index, at least at baseline and at final examination, and evaluate the data during the analysis of the study results.

G. Microbiologic Sampling

Because of the complexity of the microbial community associated with gingivitis and the difficulty in accurately ascribing causality to specific species, the FDA currently accepts microbiological data only as descriptive evidence that can be included in the *Microbiology* section of product labeling. Reductions in specific microorganisms in plaque or in the mouth cannot be a surrogate for treatment of gingivitis. However, the oral flora should be monitored to determine whether there is an increase in opportunistic or resistant organisms.

VIII. CLINICAL AND STATISTICAL SIGNIFICANCE FOR DETERMINING AN EFFECT

A. Clinical Significance

As is the case with all new drug products, the data from gingivitis studies should demonstrate that (1) the outcomes seen are unlikely due to chance (statistical significance), and (2) the magnitude of the outcomes is such that some therapeutic benefit has been established (clinical significance). In the case of gingivitis, improvement in the GI score would be a primary outcome measure (see the last paragraph in this subsection for a discussion of a meaningful improvement). To gain approval for an OTC drug claiming antigingivitis activity, the drug should also successfully demonstrate a significant PI reduction, coupled with the significant GI improvement.

For those products that treat nonplaque-induced gingivitis, demonstration of reduction in plaque may not be important. However, those products should provide convincing evidence that the underlying disease is not progressing despite abatement of the signs and symptoms. Those products probably would not be approved as OTC antigingivitis drugs. Secondary claims regarding gingival bleeding can be used in labeling if the outcomes are significant and the claims are both truthful and relevant. To avoid the bias that may result from post hoc analysis, the protocol's statistical plan should include the planned analysis of secondary outcome variables.

The Agency concurs with the consensus of the expert dental community regarding therapeutically significant improvements in plaque-induced gingivitis (see Imrey, PB, NW Chilton et al., July 1994, *Recommended Revisions to American Dental Association Guidelines for Acceptance of Chemotherapeutic Products for Gingivitis Control,* J Periodontal Res, 29(4): 299-304). Accordingly, FDA recommends that an application demonstrate the following for approval of an antigingivitis drug product:

1. The estimated proportionate reductions for the GI measurements should be no less than 15 percent in favor of the active treatment and statistically significant in each of at least two studies.

2. The arithmetic mean of the estimated proportionate reductions for the GI measurements across the studies, referred to in item #1 above, should be no less than 20 percent.

   > Proportionate reduction refers to a comparison of the active therapy to the control at the end of the study, rather than to reductions from an initial baseline level, and presumes that randomization has produced initially comparable active and control clinical samples, or that fully-appropriate statistical adjustment has been used for randomization failures (Imrey and Chilton et al., 1994).

   It is reported as a percentage and defined as:

   $$\frac{\text{(mean endpoint GI of control minus mean endpoint GI of active)}}{\text{mean endpoint GI of control.}} \times 100$$

3. Plaque reductions should be statistically significant in at least two studies. Because the exact amount of plaque reduction that is recommended for gingivitis reduction has not been established, demonstrating a statistically significant difference in plaque levels between the test group and placebo group through comparison of PI numbers is usually sufficient.

B. Statistical Considerations

In this section of the guidance document, some specific statistical considerations for gingivitis trials will be discussed. For more detail, as well as general statistical considerations in clinical

trials, refer to the ICH-E9 guidance. As discussed in the previous section, the primary efficacy variables for gingivitis trials are the GI and the PI. Statistical testing for both of these variables is usually performed with a comparison of means test through analysis of covariance.

In addition to the test of means for the GI, the sponsor can also perform a responder analysis (i.e., evaluate the GI results as a proportion of subjects or sites that achieve gingival health, as defined by a predetermined definition). For example, the number of sites at the end of the trial that measure 0 or 1 in the test group, compared to the number in the placebo group, is an outcome measure that can be evaluated. Since the goal of an antigingivitis product is to maintain gingival health, this number has a direct clinical significance that is fairly easy to interpret. If a test product can achieve 80 percent healthy sites, as compared to a placebo that only achieves 55 percent, the average practitioner may have a better understanding of the ability of the drug to maintain gingival health than would be apparent from an overall mean reduction in GI scores from 1.5 to 1.0. The traditional statistical testing for this outcome measure is a comparison of proportions of a dichotomous variable in subjects employing the Cochran Mantel Haenszel test. For comparison of sites, it may be important to conduct more complex testing, such as a repeated measures approach.

Additional indexes used as secondary outcome variables or to monitor adverse events will follow the same recommendations. Staining and calculus indexes are each evaluated as a difference in means in a similar fashion to the GI and PI, and as such are analyzed with analysis of covariance. For a site-specific dichotomous variable such as bleeding upon probing, a repeated measures approach may be appropriate.

If ethical constraints call for use of an active agent (e.g., standard of care) rather than placebo in the control arm, equivalence or non-inferiority testing can be used to compare the test product to a known effective gingivitis treatment. Non-inferiority testing is discussed in section 3.3.2 of ICH-E9. Equivalence testing is not based on a nonsignificant test result of the null hypothesis of two treatment responses being equal. An equivalence margin (i.e., the largest difference that is considered to be clinically insignificant) would be chosen.

It is generally preferable to conduct both all-randomized subjects and per protocol analyses to substantiate the study results. In superiority studies, the all-randomized subjects analysis is often more conservative than a per protocol analysis, since the noncompliers will diminish the overall treatment effect. In equivalence or non-inferiority trials, the all-randomized analysis is not conservative and may not be appropriate.

IX. SAFETY CONSIDERATIONS

Safety concerns for antigingivitis products fall into two main categories: (1) adverse events associated with the drug, and (2) masking of underlying periodontitis. Adverse events may be local events such as oral irritation or systemic events resulting from ingestion or absorption of drug. Because periodontitis may occur concurrently with gingivitis, it is important to ascertain

that treatment of the gingivitis does not conceal the more serious periodontitis from either the patient or the health care provider.

All noxious and unintended responses related to any dose of a medicinal product should be considered adverse drug reactions (see ICH guidance *E2A Clinical Safety Data Management: Definitions and Standards for Expedited Reporting*).[9] Refer to ICH-E2A for a precise definition of terms, such as mild, moderate, or severe, to describe the intensity of a specific event as well as the medical significance. Also, ICH-E1A describes the safety database for prescription products. Because OTC products usually are more widely used than prescription products and are used without professional supervision, these products may warrant a larger safety database.

We advise sponsors to develop recommendations before initiating a trial, including a policy for review of adverse events and circumstances under which a trial might be discontinued. The sponsor has an obligation to recommend and allow treatment under certain circumstances and to make provisions for emergency treatment or withdrawal from the study in the event of serious adverse reactions. In some cases, it may be appropriate to continue the subject in the trial but to modify the dosage. In the case of patient death or serious adverse events, the sponsor has specific reporting requirements, which are outlined in 21 CFR 312.32.

Since drugs are readily absorbed through the oral mucosa, the investigator should address pharmacokinetic monitoring of the drug's absorption, distribution, metabolism, and excretion at baseline and the end of the trial. It may also be advisable to consider routine laboratory screenings such as complete blood count, and measures of hepatic and renal function.

Examples of specific local adverse events associated with antigingivitis products include mucosal irritation, staining of teeth, and excessive calculus formation. Conduct of a thorough intraoral examination is desirable, beginning early in the trial to identify drug-related irritation as soon as it develops. Staining can be measured with a staining index, such as the Lobene Index done visually, or instrument-assisted colorimetric recording. Likewise, calculus can be recorded with one of several indexes. In addition, baseline and end-of-study measurement of attachment level is worthwhile in assessing whether the product has a potential to adversely affect attachment.

X. CONCLUDING COMMENTS

This guidance is not meant to be a substitute for meetings between the Agency and the drug sponsor, which are tailored to discuss a specific drug product and its precise indication. We strongly encourage the drug sponsor to take advantage of pre-investigational new drug meetings, general guidance meetings, and, particularly, end-of-phase-2 meetings before proceeding with essential clinical trials. Sponsors also can request special protocol assessments after an end-of-phase-2 meeting, which may clarify regulatory issues that were discussed during that meeting.

[9] Available on the Internet at http://www.fda.gov/cder/guidance/index.htm.

As regulatory interpretation and drug development are dynamic processes and every drug product may have unique attributes, important issues may arise that have not been addressed in this document. The procedure for scheduling and preparing for a meeting with the Agency can be found in the CDER guidance document entitled *Formal Meeting with Sponsors and Applicants for PDUFA Products.*[10] Meeting requests and requests for procedural clarification should be directed to the Supervisory Project Manager in the Division of Dermatologic and Dental Drug Products.

[10] Available on the Internet at htttp://www.fda.gov/cder/guidance/index.htm.