
Guidance for Industry

Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention

DRAFT GUIDANCE

This guidance document is being distributed for comment purposes only.

Comments and suggestions regarding this draft document should be submitted within 60 days of publication in the *Federal Register* of the notice announcing the availability of the draft guidance. Submit comments to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. All comments should be identified with the docket number listed in the notice of availability that publishes in the *Federal Register*.

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)**

**June 2005
Clinical Medical**

Guidance for Industry

Gingivitis: Development and Evaluation of Drugs for Treatment or Prevention

Additional copies of this Guidance are available from:

*Office of Training and Communications
Division of Drug Information, HFD-240
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane, Rockville, MD 20857
(Tel) 301-827-4573
<http://www.fda.gov/cder/guidance/index.htm>.*

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

**June 2005
Clinical Medical**

Contains Nonbinding Recommendations

Draft – Not for Implementation

TABLE OF CONTENTS

I.	INTRODUCTION.....	1
II.	BACKGROUND.....	2
	A. DEFINITION OF GINGIVITIS.....	2
	B. ANTINGIVITIS RULEMAKING.....	2
III.	GENERAL CONSIDERATIONS.....	3
	A. PRESCRIPTION VS. OVER-THE-COUNTER STATUS OF THE DRUG	3
	B. PREVENTION VS. TREATMENT CLAIM	3
	C. MECHANISM OF ACTION	4
	D. DOSE-RESPONSE RELATIONSHIP.....	4
	E. COMBINATION PRODUCTS.....	4
	F. ETHICAL CONSIDERATIONS OF CONDUCTING A GINGIVITIS TRIAL	4
IV.	NONCLINICAL CONSIDERATIONS	5
V.	CLINICAL PROTOCOL ISSUES AND ELEMENTS	9
	A. STUDY DESIGN	9
	B. RANDOMIZATION	9
	C. BLINDING.....	10
	D. LENGTH OF TRIAL	10
	E. STANDARD OF CARE.....	10
	F. PLACEBO OR ACTIVE CONTROL FORMULATION	11
	G. USE OF A NO-TREATMENT GROUP.....	11
VI.	CONSIDERATIONS FOR SUBJECT RECRUITMENT.....	11
	A. SAMPLE SIZE	11
	B. INCLUSION AND EXCLUSION CRITERIA	11
	C. SPECIAL POPULATIONS	14
	D. PEDIATRIC POPULATIONS	14
	E. GERIATRIC POPULATIONS	14
VII.	ASSESSMENT OF GINGIVITIS.....	15
	A. CALIBRATING INVESTIGATOR SKILLS.....	15
	B. GINGIVAL INDEX	15
	C. PLAQUE INDEX.....	16
	D. BLEEDING ON PROBING.....	16
	E. CALCULUS FORMATION	17
	F. STAINING INDEX	17
	G. MICROBIOLOGIC SAMPLING.....	17
VIII.	CLINICAL AND STATISTICAL SIGNIFICANCE FOR DETERMINING AN EFFECT	17
	A. CLINICAL SIGNIFICANCE.....	17
	B. STATISTICAL CONSIDERATIONS.....	18

IX. SAFETY CONSIDERATIONS.....	19
X. CONCLUDING COMMENTS	20

Contains Nonbinding Recommendations

Draft – Not for Implementation

Guidance for Industry¹

**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>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

34

35 **II. BACKGROUND**

36 **A. Definition of Gingivitis**

37

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

45

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

55

56 **B. Antigingivitis Rulemaking**

57

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

65

66 On May 29, 2003, the Subcommittee's final report was published in the *Federal Register* (68 FR
67 32232) as an advance notice of proposed rulemaking (ANPRM). The ANPRM established
68 conditions under which OTC drug products for the reduction or prevention of dental plaque and
69 gingivitis would be generally recognized as safe and effective and not misbranded.

70 FDA is publishing this guidance document on the development of antigingivitis drug products to
71 aid drug sponsors in conducting clinical trials either to submit additional information to the
72 antigingivitis rulemaking, or to obtain approval for a new antigingivitis drug through the NDA
73 process.

74

Contains Nonbinding Recommendations

Draft – Not for Implementation

75 **III. GENERAL CONSIDERATIONS**

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

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

84
85 Unlike a prescription drug label, an OTC label should contain indications, directions for use, and
86 warnings that are understood by the general public. Comprehension studies can demonstrate that
87 consumers will be able to understand and follow labeled directions and warnings. Sponsors of
88 OTC products should demonstrate that consumers can use these products safely since there will
89 be no health professional monitoring for adverse events or symptoms of more serious conditions,
90 such as periodontitis. Safety considerations for both prescription and OTC antigingivitis drugs
91 will be discussed in detail in section IX of this document.

92 93 **B. Prevention vs. Treatment Claim**

94
95 Another consideration is whether the therapy is intended to prevent or to treat gingivitis. Many
96 studies begin with subjects receiving a professional scaling and polishing that alone may restore
97 gingival health. The endpoint then may be the reappearance of gingivitis after a set period of
98 time. If the test group develops significantly less gingivitis than the placebo group in
99 appropriately designed studies, it is reasonable to conclude that the drug has reduced the
100 incidence of gingivitis. In the case of a chronic disease such as gingivitis, *prevention* is more
101 explicitly stated as “reduces the incidence of disease” or “reduces the incidence of severe
102 disease.” Wording that conveys this message would vary, depending on whether the product is
103 intended for prescription or OTC use. Wording for a prescription product could include
104 scientific language such as “reduction of disease incidence.” To convey this message on a level
105 more appropriate for consumers of nonprescription drugs, the Subcommittee has recommended
106 that OTC products carry the language “helps prevent gingivitis.”

107
108 Subjects who already have measurable gingivitis before treatment may experience a significant
109 reduction in the mean gingivitis score or in the number of gingivitis sites in the test group
110 compared to placebo group (scoring systems are described in section VII of this document). This
111 reduction would allow for a claim of “reduces the severity of gingivitis” or some other treatment
112 claim as appropriate for prescription or OTC status.

113

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

Contains Nonbinding Recommendations

Draft – Not for Implementation

114 **C. Mechanism of Action**

115
116 Understanding a drug's mechanism of action is desirable but not required for FDA approval for
117 marketing. There is a safety concern in treating gingivitis without removing one well-established
118 causal factor, plaque accumulation. Therefore, if the mechanism of action of the sponsor's drug
119 were other than plaque reduction (e.g., anti-inflammatory), the sponsor would be asked to
120 address the issue of masking underlying periodontitis before approval. Further discussion on this
121 topic can be found in sections VII and IX of this document.
122

123 **D. Dose-Response Relationship**

124
125 We strongly encourage the sponsor to explore the dose-response relationship early in product
126 development. It is always desirable to identify the lowest effective dose for a drug. In the case
127 of topical anti gingivitis products, not only should the lowest concentration of the drug be
128 identified, but also both the lowest effective frequency of dosing and the shortest duration of
129 therapy. As gingivitis is not a life-threatening disease and other treatments for gingivitis are
130 available, an unfavorable adverse events profile for a new anti gingivitis drug could jeopardize
131 approval, depending on the severity and seriousness of the events. A lower dose of the drug
132 might be effective and provide an appropriate safety profile.
133

134 **E. Combination Products**

135 Two or more drugs can be combined into a single dosage form when each component makes a
136 contribution to the claimed effect or effects (21 CFR 300.50 and 330.10(a)(4)(iv)). To
137 demonstrate the contribution of each component, we recommend that the combination product be
138 shown to have a greater effect than either component separately in the same vehicle, if the
139 product is for topical use. For example, if two antimicrobials are combined into one topical drug
140 product for the treatment of gingivitis, the following arms should be included in the efficacy
141 studies: vehicle, antibiotic A only in vehicle, antibiotic B only in vehicle, antibiotics A and B
142 combined. To successfully demonstrate the efficacy of A and B together, the A+B arm should
143 be significantly better at gingivitis reduction than both A alone and B alone.
144

145 **F. Ethical Considerations of Conducting a Gingivitis Trial**

146 It is important that study subjects not be exposed to permanent detrimental health outcomes as a
147 result of their participation in a clinical trial, and that subjects understand the risks and benefits
148 involved in their participation. As long as the group receiving the vehicle also receives standard
149 oral care, there is no ethical concern because gingivitis is reversible. Gingivitis trials often begin
150 with a professional oral hygiene appointment, which will benefit subjects in both the vehicle and
151 test groups.
152

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

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

160
161 In the past, experimental gingivitis models have been used to accelerate the development of
162 gingivitis to shorten the trial. Although this may be valuable during early phases of drug
163 development to determine if the test product has the potential to be effective, the ethics of this
164 approach raise concern. We recommend that sponsors carefully consider factors such as the
165 health of the subjects, duration of the proposed trial, and possibility of irreversible damage.
166 Also, these experimental gingivitis studies do not represent the natural history of gingivitis and
167 may produce misleading results.

168 169 **IV. NONCLINICAL CONSIDERATIONS**

170
171 This section of the document concerns nonclinical development issues related to products that
172 are intended for administration within the oral cavity for the treatment or prevention of
173 gingivitis. These comments are intended to supplement the applicable FDA guidance documents
174 that pertain to nonclinical development and should be considered within the context of those
175 documents.

176
177 The safety assessment of anti-gingivitis products should include consideration of the potential to
178 cause both local (inside the mouth or gastrointestinal tract) and systemic toxicity. Even if the
179 product is not intended to be swallowed, the sponsor should assume that a portion of each dose
180 will be swallowed, and many compounds are absorbed buccally or sublingually. Evaluation of
181 the systemic toxicology of compounds that are proposed for the treatment or prevention of
182 gingivitis should follow the same precepts that apply to development of the nonclinical safety
183 database associated with most other systemically administered compounds. The ICH guidance,
184 *M3 Nonclinical Safety Studies for the Conduct of Human Clinical Trials for Pharmaceuticals*,⁴
185 provides an overview of the general types of nonclinical data that may be important to support
186 various stages of clinical development and marketing of drug products. It also gives information
187 about the recommended durations of the exposures of the animals to the test materials and the
188 time at which certain nonclinical data should be available relative to clinical development. For
189 details concerning general toxicological issues, refer to the appropriate CDER guidance
190 documents.⁵

191
192 Systemic toxicity issues that concern these products are usually best assessed through toxicology
193 studies of appropriate duration and design in which the drug substance (not necessarily the drug
194 product) is administered orally (usually by gavage, but in some instances in the diet or drinking
195 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>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

206
207 For products that are intended for direct administration within the mouth, such as mouthwashes,
208 dentifrices, and intraoral sustained-release products, we recommend that sponsors consider the
209 products' potential to induce irritation or erosion of the oral tissues. The most appropriate means
210 of addressing this issue depends on the circumstances associated with a particular product and
211 clinical proposal; data from an oral irritation study conducted in animals may be unnecessary.
212 For example, if a product is very similar to a formulation that has been studied previously (in
213 animals or humans) without excessive local irritation, then additional oral irritation data may not
214 be warranted. Another factor that should be considered when assessing the importance of oral
215 irritation data in support of a given clinical proposal is the design of the proposed clinical study.
216 That is, what steps would be taken to detect oral irritation at an early stage, and what measures
217 would be taken if irritation is observed? For example, the clinical protocol may call for a
218 qualified individual to examine the oral cavity at appropriate time points (e.g., following 1, 3, 7,
219 and 14 days of treatment), with termination of dosing if signs of irritation are evident. In this
220 instance, carefully collected data from patients makes an oral irritation study in animals less
221 relevant, compared to a trial with less frequent or less comprehensive oral examinations. These
222 matters should be considered on a case-by-case basis, and the review division can be contacted
223 for specific guidance.

224
225 If it is deemed important to evaluate a product for potential to induce oral irritation in an animal
226 model, then we suggest that the following points be considered during the design of an oral
227 irritation study:

- 228
229 • **Test material.** The material that is tested should be the same formulation (including
230 inactive ingredients) that is proposed for use in humans. Sponsors should recognize
231 that inactive ingredients (e.g., alcohol, flavoring agents, surfactants) in drug products
232 are often irritating to the oral tissues.
233
- 234 • **Animals.** Rats or hamsters are generally used, although other species, such as dogs,
235 may be appropriate in certain instances. It is recommended that animals of both
236 genders be studied.
237
- 238 • **Abrasion of the mucosa.** One of the goals of an oral irritation study should be to
239 assess the product for potential to delay healing of lesions within the oral cavity.

Contains Nonbinding Recommendations

Draft – Not for Implementation

240 This goal can be accomplished by comparing the rates at which mechanically
241 induced oral lesions heal in treated and control animals. Therefore, a portion of the
242 oral mucosa of each animal should be abraded shortly before the first application of
243 the test and control materials. The buccal mucosa should be abraded on only one
244 side of the mouth, permitting examination of both intact and abraded mucosa in each
245 animal. Abrasion can be accomplished with a variety of instruments (e.g., file,
246 brush, needle). It is important that the location, size, and depth of the abrasions be as
247 uniform as possible within a study. The abrasion should be sufficiently severe that a
248 lesion extending into the sub-epithelial connective tissue is observable in tissue
249 sections from animals sacrificed 24 (or more) hours after treatment. Ideally, the
250 abrasion procedure, including the time course of the healing process, should be
251 histologically characterized before initiation of a definitive oral irritation study.
252

- 253 • **Method of application.** The test material should be applied to the oral tissues in a
254 manner that is reproducible in terms of (1) the quantity of test material that is applied
255 to the oral cavity, (2) the oral tissues to which the test material is directly applied, and
256 (3) the amount of application-induced abrasion of the oral tissues. The duration and
257 pattern of each application should be consistent. The test material is usually applied
258 with a cotton swab. In general, the animals should not be anesthetized during
259 treatment, since many anesthetics impair salivation. Placement of the test material
260 within the cheek pouch of a hamster is not particularly recommended, because the
261 amount of time that the test material is retained within the pouch may vary
262 substantially among animals (or between control and active materials). An exception
263 to this statement pertains to situations in which a solid dosage form (e.g., an osmotic
264 tablet) should be retained in the mouth for a substantial period, in which case it may
265 be appropriate to place the test material in the cheek pouch of an anesthetized hamster
266 and suture the pouch partially closed to prevent expulsion.
267
- 268 • **Dosage level.** A dosage of 1 milliliter or 1 gram of test or control material per
269 kilogram of body weight per application is generally used, although different dosage
270 volumes may be deemed appropriate on the basis of toxicity or the clinical dosage. If
271 it is considered important to examine the effect of a range of exposure levels (i.e.,
272 evaluate the dose-response relationship associated with irritation of the oral tissues),
273 the intensity or magnitude of the daily exposure to the test materials should be
274 regulated through modulation of the dosing frequency. For example, a study might
275 include a group of animals that were treated once daily, a second group that were
276 treated twice daily, and a third group that were treated four times daily. The exposure
277 level should not be modulated through variation of the quantity of material
278 administered per application, since excess test material is usually swallowed or
279 expelled without genuinely increased exposure of the oral cavity to the material.
280
- 281 • **Dosing frequency.** The number of daily applications should at least equal, and
282 preferably exceed, the maximum anticipated clinical dosing frequency for the product

Contains Nonbinding Recommendations

Draft – Not for Implementation

283 (although generally the maximum feasible number of applications per day in an
284 animal study is four, at 2-hour intervals).
285

- 286 • **Duration of application.** We recommend that the animals be treated for 28
287 consecutive days; a study of this duration should adequately support an NDA for a
288 product that is proposed for chronic use (with respect to oral irritation), since local
289 effects will be apparent within that time frame.
290
- 291 • **Controls.** The study should include a negative control group consisting of animals
292 treated with room temperature distilled water or 0.9 percent sodium chloride (NaCl).
293 The vehicle of the drug product should *not* be used as a negative control article, as
294 some inactive ingredients may be irritating.
295
- 296 • **Sacrifice schedule.** We recommend that the oral tissues be histopathologically
297 evaluated at selected intervals during the study following interim sacrifices. For
298 example, in a study in which animals are to be treated for 28 days, with the day on
299 which abrasion and the first treatments are performed being designated day 1, animals
300 might be sacrificed on days 2, 5, 29, and 43. The sacrifice on day 2 (approximately
301 24 hours after the abrasion of the mucosa) would permit assessment of the adequacy
302 and uniformity of the abrasion technique, and might involve only a small number of
303 randomly selected negative-control animals (e.g., three animals per sex). We
304 recommend that an interim sacrifice of animals in each treatment group be conducted
305 at a time point when the abraded mucosa in the negative control animals is partially
306 (but not completely) healed. The purpose of this interim sacrifice is to provide
307 information concerning the potential of the test material to delay healing of lesions of
308 the oral mucosa, which could be accomplished through comparison of the abraded
309 areas from test and control animals. Although it is suggested in this document that
310 sacrifice on day 5 *may* be appropriate for assessment of effect on healing, the
311 optimum time point will depend on various factors, including the nature of the initial
312 abrasion. The time point that is selected should be based on data from previous
313 studies that used an identical abrasion technique and evaluated the time course of
314 healing of the lesion. Animals sacrificed on day 43 (14-day recovery group) could
315 provide information about the reversibility of any lesions observed in animals
316 sacrificed on day 29.
317
- 318 • **Number of animals.** A typical study design might involve 18 animals per gender in
319 the negative control group and 15 animals per gender in each group that is to be
320 treated with a test material. Such a study could involve sacrifice of 3 negative-control
321 animals per gender 24 hours following abrasion (for assessment of the abrasion
322 technique) and 5 animals per gender from each group on the date of the interim
323 sacrifice (see the previous bulleted item above) and on days 29 and 43.
324
- 325 • **Parameters to be evaluated.** The oral cavity of each animal should be visually
326 inspected at least once daily, including evaluation of the colors of the oral tissues

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

340

V. CLINICAL PROTOCOL ISSUES AND ELEMENTS

A. Study Design

342

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

350

B. Randomization

351

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

355

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

362

- 363 • *Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*
- 364 • *Study of Drugs Likely to be Used in the Elderly*
- 365 • *ICH E11 Clinical Investigation of Medicinal Products in the Pediatric Population*

366

367

⁶Available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

369
370 In the case of an important potential confounder, such as baseline gingivitis or smoking, it may
371 be prudent to stratify the groups by this factor before randomization. In some cases, adjustments
372 for baseline characteristics may be accomplished statistically after the trial, to correct for
373 differences. If that is anticipated, characteristics should be prespecified in the statistical plan.
374 For multicenter trials, randomization of subjects within each center will help to ensure that none
375 of the centers is unbalanced in its assignment of subjects to groups. More detailed information
376 on randomization can be found in the ICH guidances, *E9 Statistical Principles for Clinical Trials*
377 and *E10 Choice of Control Group and Related Issues in Clinical Trials*.⁷

378

C. Blinding

379

380
381 We recommend a double-blinded trial design whenever possible. Should blinding be
382 compromised, the resultant bias may potentially invalidate the results. In the case of a topical
383 product, differences in packaging or discernable characteristics, such as appearance (including
384 viscosity, color, and opacity), smell, taste, or texture, may compromise blinding.

385

D. Length of Trial

386

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

399

E. Standard of Care

400

401
402 During a chronic study (6 months or longer), subjects should receive the standard of care for
403 gingivitis. This care consists of regular brushing and use of dental floss between professional
404 dental visits to maintain oral health and reduce the incidence and severity of gingivitis. Subjects
405 should be instructed to continue these measures throughout the trial. As would be typical of a
406 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>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

409

F. Placebo or Active Control Formulation

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

416

G. Use of a No-treatment Group

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

424

VI. CONSIDERATIONS FOR SUBJECT RECRUITMENT

426

A. Sample Size

428

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

438

B. Inclusion and Exclusion Criteria

440

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

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

452
453 Another consideration in OTC drug testing is the influence of confounding factors such as
454 pregnancy, diabetes, smoking, and presence of orthodontic brackets or removable prosthetic
455 appliances. Many sponsors prefer to exclude individuals with these conditions to eliminate the
456 difficulty of recording accurate measurements on them and the confounding effect of their
457 conditions on gingivitis. Excluding these individuals in a trial for an OTC product is
458 discouraged because those individuals will have access to the product in the marketplace, and the
459 study population should reflect the population that will ultimately use the product. There is
460 somewhat more flexibility in the trial of a drug that will be limited by prescription status, as the
461 prescription label can convey information to the health professional, who can then make a
462 decision about prescribing. Even in studies for prescription products, a rationale should be
463 provided for excluding some patients (e.g., known lack of efficacy, safety issues, and ethical
464 issues).

1. Recommended Inclusion Criteria

465
466
467
468 Basic conditions that are common to all gingivitis trials would include recruitment of subjects
469 who are in good general health and who have the ability to provide written informed consent.
470 Below are examples of possible inclusion criteria for gingivitis trials:

- 471
- 472 • a specified minimum number of teeth present
- 473 • a qualifying baseline plaque index
- 474 • a qualifying baseline gingival index (GI)
- 475 • presence of bleeding site or sites upon probing
- 476

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

2. Recommended Exclusion Criteria

478
479
480
481 General exclusion criteria for clinical trials can include known hypersensitivity to any
482 component of the test product or a closely related product, concomitant participation in any other
483 clinical study, or a positive urine test for drugs of abuse. Because residence in the same
484 household as a subject already enrolled in the study may create blinding and compliance issues,
485 this also may warrant exclusion from the trial.

486
487 For typical gingivitis trials, we do not recommend exclusion of subjects based on age, race, or
488 gender. Representation of special populations is expected (see section VI.C of this document
489 entitled *Special Populations*). There may be cases where pregnant subjects would be excluded
490 because of safety considerations or concerns about the confounding effect of pregnancy on
491 gingivitis; however, we discourage automatic exclusion because of pregnancy. Other exclusions
492 would depend on the drug product (e.g., gastrointestinal bleeding for an antingivitis drug that is

Contains Nonbinding Recommendations

Draft – Not for Implementation

493 a nonsteroidal anti-inflammatory). As was discussed earlier in this section of the document,
494 trials for OTC products might have fewer exclusion criteria because it is important that the
495 products be tested in a wider range of subjects. Below are examples of typical exclusion criteria
496 for gingivitis trials:
497

- 498 • Gross oral pathology, including widespread caries or chronic neglect, extensive
499 restoration, pre-existing gross plaque or calculus, or soft or hard tissue tumor of the
500 oral cavity.
501
- 502 • Chronic disease with concomitant oral manifestations.
503
- 504 • Medical conditions or significant laboratory abnormalities that the investigator
505 considers significant and that may compromise the subject's safety.
506
- 507 • Medical conditions that may affect the evaluability of the study results, such as
508 clinically significant organic disease, including heart murmur, history of rheumatic
509 fever, or valvular disease.
510
- 511 • Treatment with antibiotics within the 1-month period before the screening
512 examination, or having a condition that is likely to call for antibiotic treatment over
513 the course of the trial. This list includes cardiac conditions requiring antibiotic
514 prophylaxis, such as heart murmurs, pacemakers, or prosthetic heart valves, as well as
515 non-oral prosthetic implants.
516
- 517 • Orthodontic appliances or removable partial dentures.
518
- 519 • Periodontitis as indicated by clinical attachment loss, radiographic alveolar bone loss,
520 or periodontal pockets greater than 5 millimeters.
521
- 522 • Concomitant pharmacotherapy with drugs that may interact with test drug.
523
- 524 • Chronic treatment (2 weeks or more) with any medication known to affect
525 periodontal status (including phenytoin, calcium antagonists, cyclosporin, coumarin,
526 nonsteroidal anti-inflammatory drugs, and aspirin) within 1 month of the screening
527 examination. All other medications for chronic medical conditions have been
528 initiated at least 3 months before enrollment.
529
- 530 • History of early-onset periodontitis or acute necrotizing ulcerative gingivitis.
531
- 532 • Concomitant endodontic or periodontal therapy other than prophylaxis in the last 6
533 months.

Contains Nonbinding Recommendations

Draft – Not for Implementation

534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558

559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575

C. Special Populations

It is important to examine the effects of gender, race, and age in the clinical trials by enrolling sufficient numbers of subjects with a diverse demographic background. Although there is no evidence to demonstrate that individuals of certain races are predisposed to gingivitis, factors such as access to health care, nutritional status, and socioeconomic status may be confounding factors that affect the validity of results obtained through uneven distribution. Age and gender may affect gingivitis both physiologically and psychosocially. For example, frequency of professional visits is greater in adult women than men, and oral hygiene habits are highly inconsistent in children and adolescents. In addition, during puberty and pregnancy, hormone-associated gingivitis becomes a confounder. Furthermore — depending on the proposed therapy — drug absorption, distribution, metabolism, and excretion may be different in different races or between men and women, or between children and adults.

Smoking and diabetes are both significant risk factors for gingivitis, and it is important that they be considered in the clinical trial design. Excluding subjects with these conditions in Phase 3 studies based on lack of efficacy in these groups in Phase 2 is a possibility. The labeling may then reflect that these groups were not studied in Phase 3 after negative results in Phase 2. Stratifying by these factors is preferred because this allows study of these groups but protects against bias. Another possibility is to include all subjects but enroll a sufficient number so that they can be analyzed separately. If smokers and diabetics respond more slowly or to a lesser extent than others in the trial, this would be valuable clinical information for labeling.

D. Pediatric Populations

Gingivitis can be found in all age groups. In a comprehensive 1989 national survey conducted by the National Institute of Dental and Craniofacial Research, 47 percent of adult males and 39 percent of females exhibited at least one gingivitis site as demonstrated by bleeding on probing. Like adults, children are susceptible to plaque-induced gingivitis. The prevalence of gingivitis among school-aged children in the United States has ranged from 40 to 60 percent in national surveys. Adolescents have the highest prevalence and greatest severity of gingivitis of any age group.

Conducting clinical trials in children is challenging. Nonetheless, § 201.57(f)(9) (21 CFR 201.57(f)(9)) charges the sponsor with the provision of safety and efficacy information on children before drug approval. The pediatric plan can be tailored to the individual drug in question. If safety and/or efficacy in children cannot be extrapolated from studies in adults, it should be specifically demonstrated through enrollment of children in the same trials as adults or by conducting separate trials in children.

E. Geriatric Populations

Contains Nonbinding Recommendations

Draft – Not for Implementation

576 A *Geriatric Use* section in labeling has been a requirement for approval since August 27, 1997
577 (21 CFR 201.57(10)(ii)). Gingivitis affects individuals older than age 65 in significant numbers,
578 and these individuals may respond differently to the drug product than younger adults. We
579 encourage sponsors to (1) study a sufficient number of geriatric subjects to uncover any age-
580 related differences in safety or efficacy, and (2) describe these differences in the drug labeling.
581 For further information, including recommended labeling language, refer to § 201.57(f)(10)
582 entitled *Geriatrics Use*.

583

584 **VII. ASSESSMENT OF GINGIVITIS**

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

594

595 **A. Calibrating Investigator Skills**

596

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

608

609 **B. Gingival Index**

610

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

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

C. Plaque Index

629
630 When plaque accumulates along the tooth surface, the gingiva responds to the bacterial insult
631 with varying degrees of redness, edema, and bleeding. Regular removal of plaque through good
632 oral hygiene maintains healthy gingiva and reduces the incidence of associated gingivitis.

633
634 It is the Agency's current thinking that antigingivitis drugs using a mechanism other than plaque
635 reduction, such as anti-inflammation, could be approved as prescription drugs. However,
636 without adequate professional oversight, chronic use of an anti-inflammatory drug that does not
637 concomitantly reduce plaque has the potential to mask underlying infection. Therefore,
638 antigingivitis drugs intended for OTC use would assign PI outcome as a co-primary, rather than a
639 secondary, endpoint. This subject is discussed further in section VIII of this document.

640
641 Most trials employ a method of supragingival, rather than subgingival, plaque measurement
642 because of the difficulties in accurately observing subgingival plaque. The Turesky modification
643 of the Quigley and Hein Plaque Index has received considerable use in measuring plaque
644 changes during clinical trials. In this index, plaque is identified using a disclosing solution and
645 scored using a 0 to 5 scale in which a score of 0 corresponds to no plaque present, and a score of
646 5 designates plaque covering more than two-thirds of the tooth surface. Each tooth receives
647 mesial, middle, and distal scores for both the facial and lingual surfaces. An individual's score is
648 derived by adding the scores at each site and dividing by the number of sites evaluated. The Loe
649 and Silness Plaque Index is also used in clinical trials. It employs a scoring scale from 0 to 3 and
650 evaluates four sites on each tooth.

651
652 Sampled plaque is often weighed, either dry or wet. Note, however, that neither the PI nor
653 quantification of dry or wet plaque weight correlates strongly with gingivitis. No single
654 measurement can relate the various aspects of plaque accumulation, such as surface area of
655 plaque, mass of the plaque, density of plaque, bacterial composition, and location on the tooth.
656 The effect of plaque is most likely a combination of all these factors, which have not been
657 captured in a single index or measurement.

D. Bleeding on Probing

658
659
660
661 Bleeding on probing is a cardinal sign of gingivitis. Some GI's include an assessment of
662 bleeding. For those that do not, a categorical evaluation (yes or no) of bleeding on probing can

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

665

E. Calculus Formation

667

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

673

F. Staining Index

674

675
676 Improvement of extrinsic staining of teeth, like calculus reduction, is regarded as a cosmetic
677 claim. Also, like calculus formulation, some anti-gingivitis products are known to result in
678 increased staining on teeth. Increased staining is an adverse event that should be communicated
679 to consumers. For products thought to cause staining, it is important to obtain measurements on
680 a staining index, at least at baseline and at final examination, and evaluate the data during the
681 analysis of the study results.

682

G. Microbiologic Sampling

683

684
685 Because of the complexity of the microbial community associated with gingivitis and the
686 difficulty in accurately ascribing causality to specific species, the FDA currently accepts
687 microbiological data only as descriptive evidence that can be included in the *Microbiology*
688 section of product labeling. Reductions in specific microorganisms in plaque or in the mouth
689 cannot be a surrogate for treatment of gingivitis. However, the oral flora should be monitored to
690 determine whether there is an increase in opportunistic or resistant organisms.

691

VIII. CLINICAL AND STATISTICAL SIGNIFICANCE FOR DETERMINING AN EFFECT

693

694

A. Clinical Significance

695

696
697 As is the case with all new drug products, the data from gingivitis studies should demonstrate
698 that (1) the outcomes seen are unlikely due to chance (statistical significance), and (2) the
699 magnitude of the outcomes is such that some therapeutic benefit has been established (clinical
700 significance). In the case of gingivitis, improvement in the GI score would be a primary
701 outcome measure (see the last paragraph in this subsection for a discussion of a meaningful
702 improvement). To gain approval for an OTC drug claiming anti-gingivitis activity, the drug
703 should also successfully demonstrate a significant PI reduction, coupled with the significant GI
704 improvement.

705

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

713
714 The Agency concurs with the consensus of the expert dental community regarding
715 therapeutically significant improvements in plaque-induced gingivitis (see Imrey, PB, NW
716 Chilton et al., July 1994, *Recommended Revisions to American Dental Association Guidelines
717 for Acceptance of Chemotherapeutic Products for Gingivitis Control*, J Periodontal Res, 29(4):
718 299-304). Accordingly, FDA recommends that an application demonstrate the following for
719 approval of an antigingivitis drug product

- 720
721 1. The estimated proportionate reductions for the GI measurements should be no less
722 than 15 percent in favor of the active treatment and statistically significant in each of
723 at least two studies.
- 724
725 2. The arithmetic mean of the estimated proportionate reductions for the GI
726 measurements across the studies, referred to in item #1 above, should be no less than
727 20 percent.

728
729 Proportionate reduction refers to a comparison of the active therapy to the
730 control at the end of the study, rather than to reductions from an initial
731 baseline level, and presumes that randomization has produced initially
732 comparable active and control clinical samples, or that fully-appropriate
733 statistical adjustment has been used for randomization failures (Imrey and
734 Chilton et al., 1994).

735
736 It is reported as a percentage and defined as:

$$737 \frac{\text{(mean endpoint GI of control minus mean endpoint GI of active)}}{\text{mean endpoint GI of control.}} \times 100$$

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

746 **B. Statistical Considerations**

747
748
749 In this section of the guidance document, some specific statistical considerations for gingivitis
750 trials will be discussed. For more detail, as well as general statistical considerations in clinical

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

754
755 In addition to the test of means for the GI, the sponsor can also perform a responder analysis
756 (i.e., evaluate the GI results as a proportion of subjects or sites that achieve gingival health, as
757 defined by a predetermined definition). For example, the number of sites at the end of the trial
758 that measure 0 or 1 in the test group, compared to the number in the placebo group, is an
759 outcome measure that can be evaluated. Since the goal of an antigingivitis product is to maintain
760 gingival health, this number has a direct clinical significance that is fairly easy to interpret. If a
761 test product can achieve 80 percent healthy sites, as compared to a placebo that only achieves 55
762 percent, the average practitioner may have a better understanding of the ability of the drug to
763 maintain gingival health than would be apparent from an overall mean reduction in GI scores
764 from 1.5 to 1.0. The traditional statistical testing for this outcome measure is a comparison of
765 proportions of a dichotomous variable in subjects employing the Cochran Mantel Haenszel test.
766 For comparison of sites, it may be important to conduct more complex testing, such as a repeated
767 measures approach.

768
769 Additional indexes used as secondary outcome variables or to monitor adverse events will follow
770 the same recommendations. Staining and calculus indexes are each evaluated as a difference in
771 means in a similar fashion to the GI and PI, and as such are analyzed with analysis of covariance.
772 For a site-specific dichotomous variable such as bleeding upon probing, a repeated measures
773 approach may be appropriate.

774
775 If ethical constraints call for use of an active agent (e.g., standard of care) rather than placebo in
776 the control arm, equivalence or non-inferiority testing can be used to compare the test product to
777 a known effective gingivitis treatment. Non-inferiority testing is discussed in section 3.3.2 of
778 ICH-E9. Equivalence testing is not based on a nonsignificant test result of the null hypothesis of
779 two treatment responses being equal. An equivalence margin (i.e., the largest difference that is
780 considered to be clinically insignificant) would be chosen.

781
782 It is generally preferable to conduct both all-randomized subjects and per protocol analyses to
783 substantiate the study results. In superiority studies, the all-randomized subjects analysis is often
784 more conservative than a per protocol analysis, since the noncompliers will diminish the overall
785 treatment effect. In equivalence or non-inferiority trials, the all-randomized analysis is not
786 conservative and may not be appropriate.

IX. SAFETY CONSIDERATIONS

787
788
789
790 Safety concerns for antigingivitis products fall into two main categories: (1) adverse events
791 associated with the drug, and (2) masking of underlying periodontitis. Adverse events may be
792 local events such as oral irritation or systemic events resulting from ingestion or absorption of
793 drug. Because periodontitis may occur concurrently with gingivitis, it is important to ascertain

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

796
797 All noxious and unintended responses related to any dose of a medicinal product should be
798 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
799 of terms, such as mild, moderate, or severe, to describe the intensity of a specific event as well as
800 the medical significance. Also, ICH-E1A describes the safety database for prescription products.
801 Because OTC products usually are more widely used than prescription products and are used
802 without professional supervision, these products may warrant a larger safety database.
803

804
805 We advise sponsors to develop recommendations before initiating a trial, including a policy for
806 review of adverse events and circumstances under which a trial might be discontinued. The
807 sponsor has an obligation to recommend and allow treatment under certain circumstances and to
808 make provisions for emergency treatment or withdrawal from the study in the event of serious
809 adverse reactions. In some cases, it may be appropriate to continue the subject in the trial but to
810 modify the dosage. In the case of patient death or serious adverse events, the sponsor has
811 specific reporting requirements, which are outlined in 21 CFR 312.32.
812

813 Since drugs are readily absorbed through the oral mucosa, the investigator should address
814 pharmacokinetic monitoring of the drug's absorption, distribution, metabolism, and excretion at
815 baseline and the end of the trial. It may also be advisable to consider routine laboratory
816 screenings such as complete blood count, and measures of hepatic and renal function.
817

818 Examples of specific local adverse events associated with antigingivitis products include
819 mucosal irritation, staining of teeth, and excessive calculus formation. Conduct of a thorough
820 intraoral examination is desirable, beginning early in the trial to identify drug-related irritation as
821 soon as it develops. Staining can be measured with a staining index, such as the Lobene Index
822 done visually, or instrument-assisted colorimetric recording. Likewise, calculus can be recorded
823 with one of several indexes. In addition, baseline and end-of-study measurement of attachment
824 level is worthwhile in assessing whether the product has a potential to adversely affect
825 attachment.
826

827 **X. CONCLUDING COMMENTS**

828 This guidance is not meant to be a substitute for meetings between the Agency and the drug
829 sponsor, which are tailored to discuss a specific drug product and its precise indication. We
830 strongly encourage the drug sponsor to take advantage of pre-investigational new drug meetings,
831 general guidance meetings, and, particularly, end-of-phase-2 meetings before proceeding with
832 essential clinical trials. Sponsors also can request special protocol assessments after an end-of-
833 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>.

Contains Nonbinding Recommendations

Draft – Not for Implementation

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

¹⁰ Available on the Internet at <http://www.fda.gov/cder/guidance/index.htm>.