

listed in this paragraph (b), as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in this part, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For all antigingivitis products.* The labeling states “[bullet]¹ helps [select one of the following: ‘control,’ ‘reduce,’ or ‘prevent’] [select one or more of the following: ‘[bullet] gingivitis,’ ‘[bullet] gingivitis, an early form of gum disease,’ or ‘[bullet] bleeding gums’].”

(2) *For antigingivitis products containing stannous fluoride.* The labeling states the indication in paragraph (b)(1) of this section and/or the following: “[bullet] helps interfere with harmful effects of plaque associated with gingivitis”.

(3) *For all antigingivitis/antiplaque products.* The labeling states “[bullet] helps [select one of the following: ‘control,’ ‘reduce,’ ‘prevent,’ or ‘remove’] plaque that leads to [select one or more of the following: ‘[bullet] gingivitis,’ ‘[bullet] gingivitis, an early form of gum disease,’ or ‘[bullet] bleeding gums’].”

(c) *Warnings.* The labeling of the product contains the following warnings under the heading “Warnings”:

(1) *For all antigingivitis and antigingivitis/antiplaque products.* (i) “Stop use and ask a dentist² if [in bold type] [bullet] gingivitis, bleeding, or redness persists for more than 2 weeks [bullet] you have painful or swollen gums, pus from the gum line, loose teeth, or increasing spacing between the teeth. These may be signs or symptoms of periodontitis, a serious form of gum disease.”

(ii) The following warnings shall be used in place of the general warning statements required by § 330.1(g) of this chapter.

(A) “Keep out of reach of children under 6 years of age.” [highlighted in bold type]

(B) “If more than used for [select appropriate word: ‘brushing’ or ‘rinsing’] is accidentally swallowed, get

medical help or contact a Poison Control Center right away.”

(2) [Reserved]

(d) *Directions.* The labeling of the product states, under the heading “Directions,” the following directions for use:

(1) *For antigingivitis dentifrice products containing 0.454 percent stannous fluoride in a paste dosage form with a theoretical total fluoride concentration of 850 to 1,150 parts per million identified in § 355.10(c)(1) of this chapter.* “[bullet] adults and children 2 years of age and older: brush teeth thoroughly, preferably after each meal or at least twice a day, or as directed by a dentist or doctor [bullet] instruct children under 6 years of age in good brushing and rinsing habits (to minimize swallowing) [bullet] supervise children as necessary until capable of using without supervision [bullet] children under 2 years of age: ask a dentist or doctor”.

(2) *For antigingivitis/antiplaque oral rinse products containing 0.045 to 0.1 percent cetylpyridinium chloride.* “[bullet] adults and children 12 years of age and older: vigorously swish 20 milliliters of rinse between your teeth twice a day for 30 seconds and then spit out. Do not swallow the rinse. [bullet] children 6 years to under 12 years of age: supervise use [bullet] children under 6 years of age: do not use”.

(3) *For antigingivitis/antiplaque oral rinse products containing the combination of ingredients in § 356.26(p).* “[bullet] adults and children 12 years of age and older: vigorously swish 20 milliliters of rinse between your teeth twice a day for 30 seconds and then spit out. Do not swallow the rinse. [bullet] children 6 years to under 12 years of age: supervise use. [bullet] children under 6 years of age: do not use”.

(e) *Other information.* The labeling of the product contains the following information under the heading “Other information”:

(1) *For antigingivitis dentifrice products containing stannous fluoride.* The labeling states “[bullet] this product may produce surface staining of the teeth. Adequate tooth brushing may prevent these stains which are not harmful or permanent and may be removed by a dentist.”

(2) *For antigingivitis/antiplaque oral rinse products.* The labeling states “[bullet] this rinse is not intended to replace brushing or flossing”.

8. Section 356.66 is amended by adding paragraphs (b)(10), (c)(5), and (d)(3) to read as follows:

§ 356.66 Labeling of combination drug products.

* * * * *

(b) * * *

(10) *For permitted combinations identified in § 356.26(p).* The labeling of the product states, under the heading “Uses,” one or more of the indications for antigingivitis/antiplaque active ingredients in § 356.65(b)(3), or the following: “[bullet] helps [select one of the following: ‘control,’ ‘inhibit,’ or ‘kill’] plaque bacteria that contribute to the development of [select one or more of the following: ‘[bullet] gingivitis,’ ‘[bullet] gingivitis, an early form of gum disease,’ or ‘[bullet] bleeding gums’].”

(c) * * *

(5) *For permitted combinations identified in § 356.26.* The warnings in § 356.65(c) should be used.

(d) * * *

(3) *For permitted combinations identified in § 356.26.* The directions in § 356.65(d) should be used.

9. Section 356.92 is added to subpart D to read as follows:

§ 356.92 Testing of antigingivitis/antiplaque drug products.

The following testing should be conducted on the product formulation, a standard formulation with effectiveness documented by clinical trials, and a negative control.

(a) *Cetylpyridinium chloride rinse.* One of the following tests should be conducted:

(1) Determine the in vitro antimicrobial activity of the product against representative plaque organisms commonly associated with gingivitis. Representative organisms include, but are not limited to, typed stains of: *Actinomyces viscosus*, *Fusobacterium nucleatum*, *Porphyromonas gingivalis*, *Prevotella intermedia*, *Bacteroides forsythus*, *Candida* species, *Streptococcus mutans*, and gram negative enteric rods. Testing to determine a product's in vitro antimicrobial activity should include minimal inhibitory concentration (MIC) assays, or 30-second kill-time studies, as appropriate.

(2) Demonstrate the availability of the active ingredient using a Disk Retention Assay (DRA).

(3) Demonstrate the biological activity of the product using an ex vivo Plaque Glycolysis and Regrowth Model (PGRM).

(b) *Combination of ingredients identified in § 356.26(p).* One of the following tests should be conducted:

(1) Determine the in vitro antimicrobial activity of the product using 30-second kill-time studies with both standard laboratory strains and

¹ See § 201.66(b)(4) of this chapter for definition of bullet symbol.

² For these products, the word “dentist” should be substituted for “doctor” in the heading “Stop use and ask a doctor if” required by § 201.66(c)(5)(vii) of this chapter.