Cod liver oil
Live yeast cell derivative
Peruvian balsam
Shark liver oil
Vitamin A

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(14) of this section.

* * * * *

(13) August 5, 1991, for products subject to paragraphs (a)(26) of this section, except for those that contain live yeast cell derivative.

(14) September 2, 1994, for products subject to paragraph (a)(26)(vii) and (a)(26)(x) of this section that contain live yeast cell derivative.

Dated: August 27, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 93–21370 Filed 9–1–93; 8:45 am]

BILLING CODE 4160–01–F

---

21 CFR Part 310

[Docket No. 80N–0146]

RIN 0905–AA06

Nailbiting and Thumbsucking Deterrent Drug Products for Over-the-Counter Human Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that any nailbiting and thumbsucking deterrent drug product for over-the-counter (OTC) human use is not generally recognized as safe and effective and is misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on OTC nailbiting and thumbsucking deterrent drug products that have come to the agency's attention. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: March 2, 1994.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD–810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–594–5000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 17, 1980 (45 FR 69122), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), a proposed rule to establish a monograph for OTC nailbiting and thumbsucking deterrent drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products (the Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by January 15, 1981. Reply comments in response to comments filed in the initial comment period could be submitted by February 16, 1981.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were placed on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC nailbiting and thumbsucking deterrent drug products was published in the **Federal Register** of September 3, 1982 (47 FR 39096). Interested persons were invited to file by November 2, 1982, written comments, objections, or requests for a oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by January 2, 1983. New data could have been submitted until September 3, 1983, and comments on the new data until November 3, 1983.

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule in 21 CFR part 310 establishing that certain active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective. That final rule was effective on May 7, 1991 and included, in § 310.545(a)(13), denatonium benzoate, an active ingredient under consideration in the rulemaking for OTC nailbiting and thumbsucking deterrent drug products. This ingredient was determined to be nonmonograph because no additional data had been submitted establishing that it was generally recognized as safe and effective as a nailbiting and thumbsucking deterrent. Final agency action on all other OTC nailbiting and thumbsucking deterrent drug products occurs with the publication of this final rule.

In the proposed rule, the agency did not propose any OTC nailbiting and thumbsucking deterrent active ingredient as generally recognized as safe and effective and not misbranded. However, the agency proposed monograph labeling in the event that data were submitted that resulted in the upgrading of any ingredient to monograph status in the final rule. In this final rule, however, no active ingredient has been determined to be generally recognized as safe and effective for use in OTC nailbiting and thumbsucking deterrent drug products. Therefore, proposed subpart C of 21 CFR part 358 for OTC nailbiting and thumbsucking deterrent drug products is not being issued as a final regulation.

This final rule declares OTC drug products containing OTC nailbiting and thumbsucking deterrent active ingredients to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)), for which an application or abbreviated application (hereinafter called application) approved under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 is required for marketing. In the absence of an approved application, products containing these drugs for this use also would be misbranded under section 502 of the act (21 U.S.C. 352). In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application.

This final rule amends 21 CFR part 310 to include drug products containing nailbiting and thumbsucking deterrent ingredients by adding to subpart E new § 310.536 (21 CFR 310.536). The inclusion of OTC nailbiting and thumbsucking deterrent drug products in part 310 follows FDA's established policy for regulations in which there are no monograph conditions. (See, e.g., §§ 310.510, 310.519, 310.525, 310.526, 310.532, 310.533, and 310.534.) If, in the future, any ingredient is determined to be generally recognized as safe and effective for use in an OTC nailbiting and thumbsucking deterrent drug product, the agency will promulgate an appropriate regulation at that time.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA does not use the terms "Category I" (generally recognized as safe and

effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage. In place of Category I, the term "monograph conditions" is used; in place of Categories II or III, the term "nonmonograph conditions" is used.

In the proposed rule for OTC nailbiting and thumbsucking deterrent drug products (47 FR 39096 at 39097), the agency advised that it would provide a period of 12 months after the date of publication of the final monograph in the **Federal Register** for relabeling and reformulation of nailbiting and thumbsucking deterrent drug products to be in compliance with the monograph. Although data and information were submitted on sucrose octaacetate in response to the proposed rule, they were not sufficient to support monograph conditions, and no monograph is being established at this time. Therefore, nailbiting and thumbsucking deterrent drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions). In the proposed rule (45 FR 69122), the agency advised that conditions excluded from the monograph (Category II) would be effective 6 months after the date of publication of a final monograph in the **Federal Register**. Because no OTC drug monograph is being established for this class of drug products, the agency is adopting this 6-months effective date for the nonmonograph conditions for these drug products. Therefore, on or after March 2, 1994, no OTC drug products that are subject to this final rule may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved application.

In response to the proposed rule on OTC nailbiting and thumbsucking deterrent drug products, one State Department of Health, one drug manufacturer, and one drug manufacturer's association submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above). Additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179), or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comments

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the **Federal Register** of May 11, 1972 (37 FR 9464), and in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by informal rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y. 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).)

2. One comment contended that nailbiting and thumbsucking deterrents are not drugs within the meaning of section 201(g) of the act (21 U.S.C. 321(g)) and thus are not the proper subject of an OTC drug monograph. The comment asserted that nailbiting and thumbsucking are not "diseases" within the meaning of the act, but are instead regarded as "habits." The comment stated that the Panel found fingernail biting to be an "extremely common habit" and thumbsucking to be "a natural act of the newborn" or "an empty or simple habit as a result of learned behavior." The comment also stated that nailbiting and thumbsucking are not listed or classified in any recognized texts as diseases, but are instead regarded as habits, and quoted *Webster's Third New International Dictionary* to show that nailbiting and thumbsucking are habits and not diseases. Referring to the definition of a "drug" in section 201(g)(1)(B) of the act, the comment contended that nailbiting and thumbsucking deterrent products do not cure, mitigate, treat, or prevent a disease, and claimed that such a product "has no pharmacological effect—it just tastes bad" and thus "discourages certain bad habits." The comment argued that because these products stop a habit and a habit does not qualify as a disease, these products cannot be regulated as drugs within the meaning of the act. Several court cases were cited to support this position.

The agency has considered the above arguments and disagrees with the contention that nailbiting and thumbsucking deterrents are not drugs. As noted above, the act defines a drug, in part, in section 201(g)(1) as "* * * (B) articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man or other animals * * *."

While nailbiting and thumbsucking may be habits, they are also conditions which, if left untreated, can result in disease. The Panel (45 FR 69122 at 69123) noted that nailbiting results in fine needlelike projections at the edge of the nail which cause splits and mild paronychia (inflammation involving folds of tissue surrounding the nail). The Panel also stated that when nails are bitten excessively, open wounds result, making this area highly susceptible to infections. Nailbiting deterrents are intended to stop the "habit" and thereby prevent the disease conditions from occurring.

In its consideration of thumbsucking, the Panel referred to numerous reports showing an association of thumbsucking with malocclusion (faulty closure of upper and lower teeth) (45 FR 69122 at 69124). The Panel stated that persistent thumbsucking may lead to the incomplete eruption of the incisors as well as affect the development of muscles of the lips, thus affecting swallowing. The Panel added that arch and palate formation may be adversely affected, causing deviation of the nasal septum and mouthbreathing, and that a crossbite or other occlusal abnormalities may also develop. The Panel also stated that thumbsucking may affect respiration, mastication, speech, and swallowing (45 FR 69124). Further, the Panel stated that if thumbsucking continues past age 4 it should be treated, because continued thumbsucking may lead to clinically significant medical problems.

Promotional packaging material submitted to the Panel by a manufacturer (Ref. 1) claims that nailbiting results in harm to the digestive tract if the nails are swallowed, and that nailbiting provides a convenient entry of germs into the body, thus causing the risk of infection. The same promotional material warns against the possibility of malformation

of the bite of children whose thumbsucking habit is not stopped. Another manufacturer (Ref. 2), in its labeling submitted to the Panel, included the statement "* * * Allow the medication to dry thoroughly * * *." These labeling statements indicate that some manufacturers intend for the product to prevent disease.

Nailbiting and thumbsucking may lead to abnormal, unhealthy conditions that, if not alleviated, may cause disease. Therefore, the agency considers products used to alleviate these conditions as products intended to prevent disease. Accordingly, such products are drugs under section 201(g)(1)(B) of the act and are therefore the proper subject of an OTC drug monograph.

References

(1) OTC Vol. 160054.
(2) OTC Vol. 160010.

3. In response to an agency feedback letter to a manufacturer of nailbiting deterrent products (Ref. 1), the manufacturer asserted that nailbiting prevention products are not drugs per se and could be labeled so that they would be cosmetics under the act (Ref. 2). The manufacturer submitted examples of labeling for its products in support of this position. This comment also cited portions of a statement made by the agency in the tentative final monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products (51 FR 27346 at 27347 to 27348, July 30, 1986). The comment cited the following statement regarding dandruff shampoos in further support of its position:

> * * * the mere use of the word "dandruff" does not automatically render a shampoo or other hair care product subject to regulation as a drug. * * * When the use of the term "dandruff" deals only with appearance and not with the treatment or prevention of the underlying disease condition * * * the product is cosmetic in nature.

In order to establish the proper context for answering this comment, it is necessary to quote the entire relevant section, from which the portion was extracted in the comment. It reads as follows:

> The agency agrees with the original comment that the mere use of the word "dandruff" does not automatically render a shampoo or other hair care product subject to regulation as a drug. The Federal Food, Drug, and Cosmetic Act defines a "drug" as an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease * * * [or] intended to affect the structure or any function of the body. * * * (See 21 U.S.C. 321(g)(1)(B) and (C).) A "cosmetic," on the other hand, is defined as an article intended to be "applied to the human body * * * for cleansing, beautifying, promoting attractiveness, or altering the appearance." (See 21 U.S.C. 321(i)(1).) *The product's intended use, therefore, determines whether it is a "drug," a "cosmetic," or both. This intended use may be inferred from the product's labeling, promotional material, advertising, and any other relevant factor.* [emphasis added] See, e.g., *National Nutritional Foods Association* v. *Mathews*, 557 F.2d 325, 334 (2d Cir. 1977). When the use of the term "dandruff" deals only with appearance and not with the treatment or prevention of the underlying disease condition, as in the context that a product removes loose flakes of dandruff or cleans the hair of dandruff flakes or scales, the product is cosmetic in nature. This position is clearly and correctly stated by the agency in the letters cited by the original comment (Refs. 1 and 2).
>
> *Any use of the term dandruff that would make or imply a claim for the prevention, control, or treatment of dandruff beyond the simple mechanical removal of flakes and scales would, of course, render the product a drug. Examples of claims that would cause a hair care product to become a drug include terms such as* "antidandruff," "dandruff control shampoo," "dandruff treatment," or "*prevents dandruff.*" The agency further concludes that the differences between drug and cosmetic claims are sufficiently clear that the statement requested by the first comment is unnecessary. [emphasis added]

The labeling on nailbiting considered by the Panel, as discussed above, was clearly for the prevention of disease. The Panel believed, as does the agency, based in part on the products' marketing history, that the predominant intended use of the products was medical in nature. This pattern of use establishes the intent that brings the product within the drug definition of the act. A relevant source for determining a product's status can be the consumer's intent in using the product. The FDA is not bound by the manufacturer's subjective claims, but can find actual therapeutic intent on the basis of objective evidence. *Action on Smoking and Health* v. *Harris*, 655 F.2d 236 (DC Cir. 1980); *National Nutritional Foods Association*, supra 325, 334. While nailbiting prevention products may also be cosmetics in that they are intended to affect appearance, they nonetheless are also, and primarily, drugs because they are intended to prevent disease. As drugs, the products must be shown to be generally recognized as safe and effective or be the subject of an approved new drug application to be lawfully marketed.

With respect to the comment, this manufacturer's subjective intent too, at least up to the time that it was advised that the studies under review did not establish safety and effectiveness, as discussed below, apparently was that the products were drugs. In fact, the manufacturer submitted studies to the agency in support of OTC drug monograph status (Ref. 3). Even the labeling submitted with the comment reflects that position, especially the "Active Ingredients" section of the labeling. It is, of course, elementary that drugs have active ingredients; cosmetics have ingredients but not active ingredients.

The agency does not agree with the shampoo analogy cited by the comment with reference to the quoted extract. The claim "Stops nail biting," which is in the labeling submitted, is analogous to the shampoo claim "prevents dandruff," not "washes away flakes." And, as reference to the full passage from the quoted tentative final monograph shows, the agency concluded there that the claim "prevents dandruff" was a drug claim for a shampoo. In the current situation, the agency concludes that products intended to prevent nailbiting are drugs. Such products, depending on their labeling and other factors, may also be regulated, but not solely, as cosmetics.

References

(1) Letter from W. E. Gilbertson, FDA, to P. S. Reichertz, coded LET4, Docket No. 80N–0146, Dockets Management Branch.
(2) Letter from N. L. Buc to W. E. Gilbertson, FDA, coded LET5, Docket No. 80N–0146, Dockets Management Branch.
(3) Comment No. C00005, Docket No. 80N–0146, Dockets Management Branch.

B. Comments on Sucrose Octaacetate

4. One comment submitted data from three clinical studies to show the effectiveness of sucrose octaacetate as a nailbiting and thumbsucking deterrent (Refs. 1, 2, and 3). The comment contended that the intensely bitter taste of this ingredient is a matter of aversion therapy.

Another comment contended that "It goes without saying that any ingredient which has an intensely bitter taste which is applied to the nails (or thumbs) will deter one from placing the nail (or thumb) in his/her mouth." The comment maintained that 32 and 15 years of marketing experience for two of its products, with consumer acceptance, is a testament to their effectiveness. Based on the clinical studies and years of marketing experience, the comment concluded that there is sufficient evidence of effectiveness to place this ingredient in Category I under 21 CFR 330.10(a)(4)(ii), which states:

Effectiveness means a reasonable expectation that, in a significant proportion of the target population, the pharmacological effect of the drug, when used under adequate directions for use and warnings against unsafe use, will provide clinically significant relief of the type claimed. Proof of effectiveness shall consist of controlled clinical investigations as defined in § 314.126(b) of this chapter, unless this requirement is waived on the basis of a showing that it is not reasonably applicable to the drug or essential to the validity of the investigation and that an alternative method of investigation is adequate to substantiate effectiveness. Investigations may be corroborated by partially controlled or uncontrolled studies, documented clinical studies by qualified experts, and reports of significant human experience during marketing. * * * General recognition of effectiveness shall ordinarily be based upon published studies which may be corroborated by unpublished studies and other data.

The agency has reviewed the three clinical studies (Refs. 1, 2, and 3) and determined that the data are not adequate to support general recognition of sucrose octaacetate as safe and effective as an OTC nailbiting and thumbsucking deterrent. The data included the results of three parallel group, randomized, 6-week, placebo-controlled studies from three different research centers: (1) Marquette University School of Dentistry, (2) Eastman Dental Center, and (3) Tufts University School of Dental Medicine. (In this discussion, these studies will be referred to as the "Marquette," "Eastman," and "Tufts" studies, respectively.) These studies were designed solely to assess the effect of sucrose octaacetate during use. No attempt was made to determine the effectiveness of "aversion therapy" in changing the subjects' behavior after the drug was no longer being given.

Each study included approximately 50 subjects with a history of chronic nailbiting. Subjects were randomly assigned to treatment and placebo-control groups. The treatment groups received a solution containing sucrose octaacetate, and the control group received a solution identical in all respects but excluding sucrose octaacetate. Subjects were instructed to apply the solution to the nails at least 5 times daily and after each handwashing by brushing it over the fingernails and the surrounding skin. Subjects made entries into diaries that were collected at each weekly visit. Nails were photographed prior to the study period and at weekly intervals, using 35 millimeter (mm) film. A 1 mm standard was placed on the nail prior to photographing. The photographs were projected to a magnification of 10 times, where 1 mm was equal to 1 centimeter. Measurements were made from the cuticle to the edge of the free nail and from the cuticle to the edge of the nail bed. The length of the free nail was calculated as the difference between these two measurements. Results were evaluated by investigator examination and comparison of photographs of the nails taken prior to and during the 6-week study period. Results were expressed as mean changes in the length of the full nail (from the cuticle to the edge of the free nail) and the free nail (nailplate extending beyond the nail bed) for all five digits.

The Marquette study included 52 subjects (25 received sucrose octaacetate and 27 received placebo). Overall, 18 of 25 subjects in the treated group (72 percent) responded positively (defined as steady growth of all finger and thumb nails). In the placebo group, only 6 of 27 subjects (22 percent) responded positively. According to the sponsor, the length of free nail showed a statistically significant ($p \leq 0.001$) treatment effect at the end of 6 weeks. Mean differences between sucrose octaacetate and placebo for men and women were about 0.7 mm. The growth in full nail was also numerically greater for the treated group than for the control group, but the difference between the groups was not significant.

The Eastman study included 51 subjects. Thirty-five of the subjects were 16 years of age or younger, with 19 receiving the test solution and 16 receiving the placebo. Sixteen subjects ranged from 17 to 50 years of age, with 7 subjects receiving the test solution and 9 receiving the placebo. Weekly evaluations of nail growth were performed on the two separate age groups. No reason was given for analyzing the results as two separate groups. This analysis was not called for in the protocol. However, data on both older and younger subjects were presented. The investigator stated that statistical evaluation of the data was only done on the group aged 16 years and younger because of the wide difference in age of the older group. In contrast to the other two studies, only the data on total nail growth of all nails over the entire test period for each subject were provided. Free nail growth was not calculated. Calculation of the free nail growth (done in the other studies) requires careful photographing to insure sharpness, color reproducibility, and consistency. Many of the subjects in this study used nail polish, sometimes making measurement of the free nail impossible. Analysis of the data from the younger group showed no significant differences in total nail growth between the test and control groups. Thus, the study does not support the effectiveness of the product as a nailbiting deterrent.

The Tufts study enrolled 50 subjects, 29 in the test group and 21 in the placebo group. This study included a minimum of 5 weeks of observation as opposed to the 6 weeks called for in the protocol. By the Mann-Whitney U test, statistically significant differences were seen at 5 weeks in both the free nail ($p < 0.0001$) and the full nail ($p < 0.0003$) analyses. The control group showed a relatively large response to the placebo during the first 3 weeks, after which growth leveled off. The nails of the test group continued to improve so that the test group and the control group differed significantly after 3 weeks for free nails and after 4 weeks for full nails. P values were supplied for the treatment by period interaction. They were statistically significant.

The Marquette and Tufts studies appear to suggest some effect of sucrose octaacetate in decreasing nailbiting during use. Apart from the questionable relevance of the finding to the use of such products (discussed below), the agency cannot conclude that the two studies are well-controlled clinical trials. Important details are lacking about the conduct of the studies: (1) The method of randomization was not provided. Although random treatment allocation appears to have been used, in the Tufts study missing participant numbers, use of the same number for two people, and the imbalance between the groups (29 vs 21) raise questions about failure of randomization, omission of or addition of participants, errors, or dropouts. (2) The reports do not indicate whether or not the photographs of the fingernails were interpreted with the observer unaware of treatment assignment, which is critical to determining whether potential observer biases were minimized. (3) It is not clear what was the primary end point, total or free nail growth. How the two measures differ and their independence was not clearly discussed. (4) Subjects' responses, other than those relating to nail growth, were not evaluated.

A number of subjects, in their diary entries, alluded to perceived adverse changes in the appearance or consistency of the nail, a disappearance or decrease in intensity of the bad taste with time, a switch from nailbiting to tearing at soft tissue, and/or an irritation of open wounds. These and any other adverse effects were ignored in the reports and summary, which did not acknowledge that unwanted effects may or may not have been present. The studies thus fail to adequately assess the

safety of sucrose octaacetate. Although the two studies appear to confirm one another, the investigators expressed the results in different ways: change, total length differences. Thus, it is difficult to directly compare results.

The 6-week duration of the studies and the failure to follow subjects off treatment allows assignment only of a short-term effect of sucrose octaacetate as a nailbiting deterrent. As stated in the comment, the objective of using sucrose octaacetate (bitter taste) is to break the nailbiting habit through aversion therapy, an action that can only be evidenced if subjects stop using the sucrose octaacetate and a persistent effect on the nailbiting habit is clearly shown. The product is not intended to be used indefinitely. The design of further studies should reflect the therapeutic goal; i.e., the studies need to show effects on nailbiting persisting after use of the drug is completed.

While some of the submitted studies might, if described more fully, suggest that sucrose octaacetate has a small effect on nailbiting while being used, there is no evidence that the effect persisted after the treatment was stopped or that the drug has an effect on breaking the nailbiting habit. Accordingly, the agency is not including sucrose octaacetate in this final rule as a monograph ingredient.

References

(1) Azhdari, S. S., "Nail Biter Sucrose Octa Acetate Efficacy Study," unpublished study in Comment No. C00005, Docket No. 80N–0146, Dockets Management Branch.

(2) Johnson, E., S. Schwartz, and R. E. Clark, "Placebo-controlled, Double Blind, Parallel Group Evaluation of the Efficacy of Sucrose Octa Acetate (SOA) in Suppression of Nail Biting," unpublished study in Comment No. C00005, Docket No. 80N–0146, Dockets Management Branch.

(3) Sveen, O. B., "Sucrose Octa Acetate Efficacy Study," unpublished study in Comment No. C00005, Docket No. 80N–0146, Dockets Management Branch.

5. One comment contended that the results of studies designed to assess the effectiveness of sucrose octaacetate as a nailbiting deterrent (specifically, the three studies discussed in comment 3) could also be related to thumbsucking because the drug works by a conditioning action.

The agency does not agree with the comment. In discussing testing guidelines, the Panel specifically stated that a double-blinded study, using the vehicle as a control, in a patient population of nailbiters as well as thumbsuckers was needed (45 FR 69122 at 69127). The three studies contained data only on nailbiting. The agency agrees that the results of studies done on a nailbiting population, even if persuasive for effectiveness in that condition, would not constitute evidence of effectiveness as a thumbsucking deterrent. Moreover, the supposed similar effects are based on the idea that a "conditioning" action would be effective in both conditions; in fact, the nailbiting studies cannot provide support for such an effect because sucrose octaacetate was used throughout the study. The agency is not aware of any basis for assuming that the drive or motivation for nailbiting would be equal in magnitude to that for thumbsucking and that, consequently, the same adverse taste would equally deter both habits. The thumb is in the mouth longer during thumbsucking than is the finger during nailbiting. Phenomena such as tolerance or tachyphylaxis could therefore be important to different extents in nailbiters and thumbsuckers. Comments recorded in the diaries of a number of the subjects in the studies indicated that the bitter taste of sucrose octaacetate either vanished completely or was materially changed in intensity with time, suggesting that tolerance might occur. Thumbsuckers who are strongly driven may tolerate the few minutes of adverse effect in order to derive the longer-term (presumed) benefit of thumbsucking.

The submitted data did not include any direct assessment of sucrose octaacetate as a deterrent for thumbsucking, nor any evidence of a "conditioning" effect in any setting. The agency has no basis for assuming that the bitter taste of sucrose octaacetate would have a favorable short- or long-term effect on thumbsucking.

C. Comments on Labeling

6. Several comments discussed suggested labeling for OTC nailbiting and thumbsucking deterrent drug products. Because no active ingredients have been classified as a monograph condition in this final rule for OTC nailbiting and thumbsucking deterrent drug products, the agency is not addressing the comments' requests. Data in the form of a new drug application or a petition to establish a monograph, pursuant to 21 CFR 10.30, may be submitted to support an ingredient's safety and effectiveness as a nailbiting and/or thumbsucking deterrent. Should such data demonstrate an ingredient's safety and effectiveness for this use, the agency will then consider labeling recommendations such as those made by the comments.

II. The Agency's Final Conclusions on OTC Nailbiting and Thumbsucking Deterrent Drug Products

At this time, there is a lack of data from adequate and well-controlled, double-blind studies to establish that denatonium benzoate, sucrose octaacetate, or any other ingredients are safe and effective for use as a nailbiting or thumbsucking deterrent. The agency has determined that no active ingredient has been found to be generally recognized as safe and effective for OTC use as a nailbiting or thumbsucking deterrent.

In the **Federal Register** of November 7, 1990 (55 FR 46914), the agency published a final rule in 21 CFR part 310, establishing that certain active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective. That final rule was effective on May 7, 1991, and included in § 310.545(a)(13) the ingredient denatonium benzoate that had been previously considered under this rulemaking for use as a nailbiting or thumbsucking deterrent. The final rule in this document establishes that any OTC nailbiting or thumbsucking deterrent drug product is not generally recognized as safe and effective and expands the nonmonograph ingredients to include all other nailbiting and thumbsucking deterrent active ingredients, such as sucrose octaacetate. Therefore, any ingredient that is labeled, represented, or promoted for OTC use as a nailbiting or thumbsucking deterrent is considered nonmonograph and misbranded under section 502 of the act and is a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 of the regulations is required for marketing. In appropriate circumstances, a citizen petition to establish a monograph may be submitted under 21 CFR 10.30 in lieu of an application. Any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action. In order to avoid duplication in listing OTC nailbiting and thumbsucking active ingredients in more than one regulation and for ease in locating these ingredients in the CFR, the agency is listing all of these ingredients in a single regulation in 21 CFR 310.536 entitled "drug products containing active ingredients offered over-the-counter (OTC) for use as a

nailbiting or thumbsucking deterrent." Accordingly, § 310.545(a)(13) is being removed.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (47 FR 39096 at 39098). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that not one of these rules, including this final rule for OTC nailbiting and thumbsucking deterrent drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96–354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC nailbiting and thumbsucking deterrent drug products is not expected to pose such an impact on small businesses because only a limited number of products are affected. As noted above, the ingredient denatonium benzoate has already been removed from OTC nailbiting and thumbsucking deterrent drug products. The agency is only aware of several products that contain the ingredient sucrose octaacetate. The agency is aware of one product that contains the ingredient cayenne pepper as the listed active ingredient. Based on the limited number of affected products, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

The agency has determined under 21 CFR 25.24(c)(6) that this action is of a type that does not individually or cumulatively have a significant effect on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

List of Subjects in 21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR part 310 is amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 721 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 379e); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.536 is added to subpart E to read as follows:

§ 310.536 Drug products containing active ingredients offered over-the-counter (OTC) for use as a nailbiting or thumbsucking deterrent.

(a) Denatonium benzoate and sucrose octaacetate have been present in OTC nailbiting and thumbsucking deterrent drug products. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these and any other ingredients (e.g., cayenne pepper) for OTC use as a nailbiting or thumbsucking deterrent. Based on evidence currently available, any OTC drug product containing ingredients offered for use as a nailbiting or thumbsucking deterrent cannot be generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, and promoted as a nailbiting or thumbsucking deterrent is regarded as a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) for which an approved application or abbreviated application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application or abbreviated new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for OTC use as a nailbiting or thumbsucking deterrent is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After March 2, 1994, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

§ 310.545 [Amended]

3. Section 310.545 *Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses* is amended by removing and reserving paragraph (a)(13).

Dated: August 26, 1993.

Michael R. Taylor,

Deputy Commissioner for Policy.

[FR Doc. 93–21371 Filed 9–1–93; 8:45 am]

BILLING CODE 4160–01–F