DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 357

[Docket No. 81N-0027]

Smoking Deterrent Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of a tentative final monograph that would establish conditions under which over-the-counter (OTC) smoking deterrent drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products and public comments on an advance notice of proposed rulemaking that was based on those recommendations. This proposal in part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by September 3, 1985. New data by July 3, 1986. Comments on the new data by September 3, 1986. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by October 31, 1985.

ADDRESS: Written comments, objections, new data, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 5, 1982 (47 FR 490) FDA published, under §330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC smoking deterrent drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products, 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 April 5, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by May 5, 1982.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information. In response to the advance notice of proposed rulemaking, two drug manufacturers and one consumer submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

In order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10), the present document is designated as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Part 357 (21 CFR Part 357), FDA states for the first time its position on the establishment of a monograph for OTC smoking deterrent drug products. Final agency action on this matter will occur with the publication at a future date of a final rule for OTC smoking deterrent drug products.

This proposal constitutes FDA's tentative adoption of the Panel's conclusions and recommendations on OTC smoking deterrent drug products as modified on the basis of the comments received and the agency's independent evaluation of the Panel's report. Modifications have been made for clarity and regulatory accuracy and to reflect new information. Such new information has been placed on file in the Dockets Management Branch (address above). These modifications are reflected in the following summary of the comments and FDA's responses to them.

The OTC procedural regulations (21 CFR 330.10) have been revised to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). (See the **Federal Register** of September 29, 1981; 46 FR 47730.) The Court in *Cutler* held that the OTC drug review regulations were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision has been deleted from the regulations, which 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.

Although it was not required to do so under *Cutler*, FDA will no longer 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, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (Old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register**. On or after that date, no OTC drug products that are subject to the monograph and that contain nonmonograph conditions, i.e., conditions that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to this monograph that are repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In the advance notice of proposed rulemaking for OTC smoking deterrent drug products (published in the **Federal Register** of January 5, 1982; 47 FR 490), the agency suggested that the conditions included in the monograph (Category I) be effective 6 months after the date of publication of the final monograph in the **Federal Register**. Experience has shown that relabeling of products covered by the monograph is necessary in order for manufacturers to comply with the monograph. New labels containing the monograph labeling have to be written,

ordered, received, and incorporated into the manufacturing process. The agency has determined that it is impractical to expect new labeling to be in effect 6 months after the date of publication of the final monograph. Experience has shown also that if the deadline for relabeling is too short, the agency is burdened with extension requests and related paperwork.

In addition, some products may have to be reformulated to comply with the monograph. Reformulation often involves the need to do stability testing on the new product. An accelerated aging process may be used to test a new formulation; however, if the stability testing is not successful, and if further reformulation is required, there could be a further delay in having a new product available for manufacture.

The agency wishes to establish a reasonable period of time for relabeling and reformulation in order to avoid an unnecessary disruption of the marketplace that could not only result in economic loss, but also interfere with consumers' access to safe and effective drug products. Therefore, the agency is proposing that the final monograph be effective 12 months after the date of its publication in the **Federal Register.** The agency believes that within 12 months after the date of publication most manufacturers can order new labeling and reformulate their products and have them in compliance in the marketplace. However, if the agency determines that any labeling for a condition included in the final monograph should be implemented sooner, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set for removal of that condition from OTC drug products.

In the event that new data submitted to the agency during the alloted 12-month comment and new data period are not sufficient to establish "monograph conditions" for OTC smoking deterrent drug products, the final rule will declare these products to be new drugs under section 201(p) of the Federal Food, Drug, and Cosmetic Act, for which new drug applications approved under section 505 of the act and 21 CFR Part 314 are required for marketing. Such rule will also declare that in the absence of an approved new drug application, these products would be misbranded under section 502 of the act. The rule will then be incorporated into 21 CFR Part 310, Subpart E—Requirements for Specific New Drugs or Devices, instead of into an OTC drug monograph in Part 357.

I. The Agency's Tentative Conclusions on the Comments

1. One comment cited an apparent inconsistency between the Panel's recommended objective of a clinical study and the indications recommended by the Panel for smoking deterrent drug products. Under the Panel's proposed testing guidelines, effectiveness is measured only in terms of the number of subjects who "stopped smoking," yet the allowable label claims are couched in such terms as "a temporary aid" and "helps stop temporarily." The comment stated that if the protocol is designed to measure only such absolutes as "stops smoking" then labeling claims that are consistent with those results should also be allowed.

Several comments objected to the position taken by the Panel that "reduction of the number of cigarettes smoked or limited cessation of smoking" is not an aid to stopping smoking and is of little value. The comments argued that a reduction in smoking has not been scientifically demonstrated to be of no help in aiding one to stop smoking. The comment stated that a significant reduction in the number of cigarettes smoked indicates that an aversion to cigarettes has been established and that a substance that could do this, with supplemental motivation, would fulfill its function as a "temporary aid."

The agency recognizes that the Panel's recommended primary objective of a clinical study, i.e., to determine the effectiveness of the drug under study in aiding one to stop smoking, may appear to be inconsistent with the recommended indications for use and with the definition of smoking deterrents where terms such as, "a temporary aid," "helps stop temporarily," etc. are used. Although the desired effect of the drug is to stop the user of the drug from smoking by altering the tobacco taste so that smoking becomes unpleasant and undesirable or by producing tobacco satiety without smoking, the Panel believed that the labeling should reflect and emphasize to the consumer that the product is only for temporary use. However, the agency recognizes that there may be confusion with respect to two of the Panel's recommended Category I labeling indications, i.e., "Helps you stop the cigarette urge temporarily," and "Helps you stop smoking cigarettes temporarily," because the placement of the word "temporarily" does not adequately reflect the intended use and effect of the drug. For this reason the agency is not including these two indications in the tentative final monograph. The agency believes that recommended §§ 357.650(b)(1) and (4), i.e., "A temporary aid to those who want to stop smoking cigarettes," and "A temporary aid to breaking the cigarette habit," more accurately reflect the intended use of the product. The agency has also revised the definition of smoking deterrent to read as follows: *"Smoking deterrent.* A substance that is used temporarily to help those individuals who want to stop smoking (become cigarette free) or to break the cigarette habit."

The agency is aware that recent reports in the literature have indicated that reduction in smoking, or controlled smoking, should be considered as an alternative to abstinence, because of the generally disappointing outcomes of traditional abstinence-oriented smoking-treatment studies (Refs. 1, 2, and 3). One such report analyzed a number of subjects throughout the period of follow-up that were either abstinent or nonabstinent after undergoing treatment. The authors concluded that abstinence and reduction are not necessarily different points on the same continuum, but rather that abstinence and smoking reduction should be treated as two potentially discrete treatment outcomes (Ref. 4). Reduction in smoking may be achieved by decreasing the number of cigarettes smoked or by switching to a low nicotine-low tar (LN/LT) cigarette. However, evidence on the effects of controlled smoking on the health of the individual smoker has been contradictory. Some studies indicate that although smokers may reduce the number of cigarettes smoked or progressively switch to LN/LT cigarettes, they inadvertently increase their puff volume, puff frequency, or depth of inhalation and thereby increase smoke-related health risks (Refs. 5 through 8). Other studies suggest that smokers who reduce the numbers of cigarettes or switch to LN/LT cigarettes do not compensate by increasing puff volume, frequency, or depth of inhalation (Refs. 1, 2, 3, 9, 10, and 11). Even so, there is insufficient evidence to show that a significant reduction in smoking will lead to cessation or that reduction will lower the health risks associated with smoking (Ref. 8). If sufficient evidence becomes available demonstrating that a reduction in smoking results in a significant health benefit to consumers, then well-controlled studies to establish the safety and efficacy of smoking deterrent drug products in reducing smoking will be needed. These studies should include appropriate objective measurements that account for compensatory behavior

in smoking and should be of sufficient length so that the results are meaningful.

Because of a lack of adequate data, the agency is not including smoking reduction claims in this tentative final monograph. Should sufficient data regarding reduction claims become available before the publication of the final monograph, the agency will consider including reducing in smoking claims in the final monograph.

References

(1) Prue, D. M., et al., "Carbon Monoxide Levels and Rates of Consumption After Changing to Low Tar and Nicotine Cigarettes," *Behaviour Research and Therapy*, 21:201–207, 1983.

(2) Prue, D. M., et al., "Brand Fading: The Effects of Gradual Changes to Low Tar and Nicotine Cigarettes on Smoking Rate, Carbon Monoxide, and Thiocyanate Levels," *Behavior Therapy*, 12:400–416, 1981.

(3) Foxx, R. M., and R. A. Brown, "Nicotine Fading and Self-Monitoring for Cigarette Abstinence or Controlled Smoking," *Journal of Applied Behavior Analysis*, 12:111–125, 1979.

(4) Poole, A. D., et al., "The Rapid-Smoking Technique: Subject Characteristics and Treatment Outcome," *Behavior Research and Therapy*, 20:1–7, 1982.

(5) Herning, R. I., et al., "How a Cigarette is Smoked Determines Blood Nicotine Levels," *Clinical Pharmacology and Therapeutics*, 33:84–90, 1983.

(6) Ho-Yen, D. O., et al., "Why Smoke Fewer Cigarettes?" *Pharmacology Biochemistry and Behavior*, 17:1905–1907, 1982.

(7) Russell, M. A. H., "Realistic Goals for Smoking and Health—A Case for Safer Smoking," *Lancet*, 1:254–257, 1974.

(8) "The Changing Cigarette. A Report of the Surgeon General," U.S. Department of Health and Human Services, DHHS Publication No. (PHS) 81–50156., U.S. Government Printing Office, Washington, DC, 1981.

(9) Foxx, R. M., and E. Axelroth, "Nicotine Fading, Self-Monitoring and Cigarette Fading to Produce Abstinence or Controlled Smoking," *Behavior Research and Therapy*, 21:17–27, 1983.

(10) Stitzer, M. L. and G. E. Bigelow, "Contingent Reinforcement for Reduced Carbon Monoxide Levels in Cigarette Smokers," *Addictive Behaviors*, 7:403–412, 1982.

(11) Bernard, H.S., and J.S. Efran, "Case Histories and Shorter Communications: Eliminating Versus Reducing Smoking Using Pocket Timers," *Behavior Research and Therapy*, 10:399–401, 1972.

2. Several comments objected to the Panel's recommended guidelines for developing protocols for evaluating OTC smoking deterrents. The comments gave the following reasons: (1) The recommended guidelines are unduly detailed and demanding and impose costly drug testing; (2) the guidelines require that all smoking deterrents meet the same criteria and do not allow for differences in mechanism of action and length of use time; (3) the guidelines do not include a parameter for assessing the subjects compliance to therapeutic regimen or control for the significant variability of tar, nicotine, and other ingredients found in different types of cigarettes; (4) the guidelines fail to establish the meaning of the terms "clinically significant," as they do "statistically significant;" (5) the measurements of thiocyanate and cotinine should be preferred because measurements for carbon monoxide are not a reliable indication of smoking; and (6) the requirement that two separate clinical trials should be conducted by different investigators at different geographical sites is excessive for old drugs not subject to an NDA.

The agency has not addressed specific testing guidelines in this document. In revising the OTC drug review procedures relating to Category III, published in the **Federal Register** of September 29, 1981 (46 FR 47730), the agency advised that tentative final and final monographs will not include recommended testing guidelines for conditions that industry wishes to upgrade to monograph status. Instead, the agency will meet with industry representatives at their request to discuss testing protocols. On the same date, the agency also published in the **Federal Register** a policy statement relating to a number of matters involving the testing of Category III ingredients (46 FR 47740) including meetings with industry or other interested persons. (See also part II. paragraph 2 below—Testing of Category II and Category III conditions.)

3. One comment stated that the labeling of a lobeline sulfate-containing product did not include warnings or cautions against the use of the product while taking other medications. The individual submitting the comment reported personally experiencing the symptoms of vomiting, faintness, blurred vision, stomach cramping, and dehydration after taking a lobeline sulfate-containing product for a week while also taking Dyazide® and Valium®. The comment urged the agency to establish rules requiring manufacturers and distributors to label the products clearly as to identity, contraindications or precautions, and particularly to include warnings concerning interactions with other medications.

The agency agrees with the comment that the labeling of OTC drug products should contain the necessary information needed to use the drug safely. Under current regulations, all OTC drug products are required to list the active ingredients on the label. The agency has fully evaluated the case report submitted in the comment. However, the facts in the case are such that a clear association between concomitant use of the drugs and the symptoms that occurred cannot be established. The agency is aware, however, that lobeline sulfate can cause gastrointestinal side effects and notes that for this reason some marketed products include buffering ingredients. In addition, in its discussion on the safety of lobeline sulfate (47 FR 496) the Panel noted that the symptoms of stomach ache, severe heartburn, nausea, vomiting, and faintness have been reported from a single dose of 8 milligrams (mg) lobeline sulfate. Because lobeline sulfate can cause side effects, the agency believes that a warning may be appropriate.

However, because lobeline sulfate is not Category I at this time, the agency is not proposing a warning statement in this tentative final monograph. In the event that lobeline sulfate reaches monograph status the agency will consider including a warning statement in a final monograph at that time.

4. One comment objected to the Panel's Category II classification of silver nitrate on the basis that it was not able to locate any significant body of data demonstrating the safety and effectiveness of silver nitrate when used as an OTC smoking deterrent. The firm submitting the comment stated that it has been active in developing a mouthrinse utilizing silver nitrate as an active ingredient for use as an OTC smoking deterrent. The comment submitted two studies that it contends clearly demonstrate the efficacy of silver nitrate as a smoking deterrent (Ref. 1). The comment also asserted that the Panel failed to discuss smoking deterrents in aqueous mouthrinse form, which it contended is more appropriate and more effective in treating the problem of smoking. Additionally, the comment stated that because silver appears to have a low systemic toxicity and because the Panel did not list any potential safety problem with respect to the use of silver nitrate in a smoking deterrent drug product, the findings of safety with respect to silver acetate should be also applied to silver nitrate. The comment requested that silver nitrate be reclassified from Category II to the same Category as that for silver acetate so that testing already begun may be completed.

The agency notes that the Panel's report does not discuss nor does the recommended monograph require that

smoking deterrent active ingredients be administered in any specified oral form. The only requirement for form of administration of an OTC drug is that the vehicle of administration be safe and that it not interfere with the safety and effectiveness of the active ingredient.

The agency further notes that although the studies submitted were intended as support for the safety and efficacy of silver nitrate, the drug used in the studies was described as a povidone-silver nitrate preparation (Ref. 1). Therefore, the studies cannot be used in support of silver nitrate as an OTC smoking deterrent. Because no data were submitted to the Panel and no data have been submitted to the agency to support the use of silver nitrate as a single active ingredient for use as an OTC smoking deterrent, the agency concurs with the Panel that silver nitrate should be Category II. Additionally, the agency is not aware of the marketing in the United States of any OTC smoking deterrent drug product containing povidone-silver nitrate as an active ingredient. Accordingly, the agency is unable to determine at this time that the ingredient is generally recognized as safe and effective as an OTC smoking deterrent. Morever, povidone-silver nitrate has not been marketed to a material extent or for a material time in the United States for use OTC smoking deterrent drug products. Therefore, the agency considers this ingredient to be a new drug within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321(p)). The ingredient may not be marketed as a smoking deterrent until FDA has approved an NDA for such use.

Reference

(1) Comment No. C00001, Docket No. 81N-0027, Dockets Management Branch.

II. The Agency's Tentative Adoption of the Panel's Report

A. Summary of Ingredient Categories and Testing of Category II and Category III Conditions.

1. *Summary of ingredient categories.* The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and concurs with the Panel's classification of these ingredients. For the convenience of the reader the following table is included as a summary of the categorization of OTC smoking deterrent active ingredients.

Smoking deterrent active ingredients	Panel	Agency
Cloves, ground	II	II
Coriander, ground	II	II
Eucalyptus oil	II	II
Ginger, ground Jamaica	II	II
Lemon oil, terpeneless	II	II
Licorice root extract	II	II
Lobeline (in the form of lobeline sulfate or its pharmocological equivalent as natural lobelia alkaloids or *Lobelia inflata* herb.	III	III
Menthol	II	II
Methyl salicylate	II	II
Povidone-silver nitrate		New drug.
Quinine ascorbate	II	II
Silver acetate	III	III
Silver nitrate	II	II
Thymol	II	II

The agency is not aware of any data demonstrating the safety and effectiveness of any ingredient not listed above for OTC use as a smoking deterrent drug product including those listed in the Panel's report at 47 FR 492, part I, paragraph C.2. Therefore, the agency classifies all other ingredients as Category II for this use.

2. *Testing of Category II and Category III conditions.* The Panel recommended testing guidelines for OTC smoking deterrent drug products (47 FR 498). The agency is offering these guidelines as the Panel's recommendations without adopting them or making any formal comment on them. Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any smoking deterrent ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). This policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency Changes.

FDA has considered the comments and other relevant information and concludes that it will tentatively adopt the Panel's report and recommended monograph with the changes described in FDA's responses to the comments above and with other changes described in the summary below. A summary of the changes made by the agency follows.

1. The indications "Helps you stop the cigarette urge temporarily" and "Helps you stop smoking cigarettes temporarily" have not been included in the monograph. (See comment 1 above.)

2. The definition of smoking deterrent has been changed. (See comment 1 above.)

3. Because there are no Category I ingredients and because the purpose of an OTC drug monograph is to set forth those specific conditions under which OTC drugs are generally recognized as safe and effective and not misbranded, the agency is not proposing in this tentative final monograph the labeling recommended by the Panel in § 357.650(b)(6) (mechanism of action labeling). Should data establishing the safety and effectiveness of any smoking deterrent active ingredient be submitted during the allotted 12-month comment and new data period, the agency will consider appropriate mechanism of action claims for inclusion in the final monograph.

4. The statement "This product's effectiveness is directly related to the user's motivation to stop smoking cigarettes" has not been included in the tentative final monograph. The agency believes the statement is unnecessary because it is similar to information already contained in the indications.

During the course of the OTC drug review, the agency has maintained that the terms that may be used in an OTC drug product's labeling are limited to those terms included in a final OTC drug monograph. (This policy has become known as the "exclusivity rule.") The agency's position has been that it is necessary to limit the acceptable labeling language to that developed and approved through the OTC drug review process in order to ensure the proper and safe use of OTC drugs. The agency has never contended, however, that any list of terms developed during the course of the review exhausts all the possibilities of terms that appropriately can be used in OTC drug labeling. Suggestions for additional terms or for other labeling changes may be submitted as comments to proposed or tentative final monographs within the specified time periods or through petitions to amend monographs under § 330.10(a)(12).

During the course of the review, FDA's position on the "exclusivity rule" has been questioned many times in comments and objections filed in response to paticular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. In a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002), FDA announced that a hearing would be held to assist the agency in resolving this issue. On September 29, 1982, FDA conducted an open public forum at which interested parties presented their views. The forum was a legislative type administrative hearing

under 21 CFR Part 15 that was held in response to a request for a hearing on the tentative final monographs for nighttime sleep-aids and stimulants (published in the **Federal Register** of June 13, 1978; 43 FR 25544).

After considering the testimony presentd at the hearing and the written comments submitted to the record, in the **Federal Register** of April 22, 1985 (50 FR 15810), FDA proposed to change its exclusivity policy for the labeling of OTC drug products. As proposed, manufacturers may select one of the following options:

(1) The label and labeling would contain within a boxed area designated "APPROVED USES" the specific wording on indications for use established under an OTC drug monograph. The boxed area would be required to be displayed in a prominent and conspicuous location. As under the present policy, the labeling in the boxed area would be required to be stated in the exact language of the monograph. However, with this option a statement that the information in the box was published by the Food and Drug Administration would appear either in the box or reasonably close by. At the manufacturer's option, the designation of the boxed area and the statement that the labeling was established by FDA could be combined.

(2) As a complete alternative to using the boxed area designated "APPROVED USES," the proposal would for the first time allow manufacturers an option to use other truthful and nondeceptive statements relating only to the indications established in an applicable monograph subject to the prohibitions in section 502(a) of the act against misbranding by the use of false or misleading labeling. If this alternative is selected, the manufacturer would not be able to use a boxed area or include a statement that the indications are endorsed by the Food and Drug Administration.

(3) As third alternative, manufacturers could use both a boxed area with the monograph language and also, elsewhere in the labeling, use other non-monograph language that meets the statutory standards of truthfulness and accuracy.

Regardless, other aspects of OTC drug labeling, such as the statement of identity, warnings, and directions, would continue to be required to comply with the monograph, including following any exact language established in the monograph.

The proposal to change the exclusivity policy provides for 90 days of public comment. After considering all comments submitted, the agency will announce its final decision on this matter, in a future issue of the **Federal Register.**

The agency has examined the economic consequences of this proposed rulemaking 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 none of these rules, including this proposed rule for OTC smoking deterrent drug products, is a major rule.

For purposes of the Regulatory Flexibility Act, Public Law 96-354, the economic assessment concluded that, while the average economic impact of the overall OTC drug review on small entities will not be significant, the possibility of larger-than-average impacts on some small firms in some years might exist. Therefore, the assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose a significant impact on a substantial number of small entities. The analysis identified the possibilities of reducing burdens on small firms through the use of (a) relaxed safety and efficacy standards or (b) labels acknowledging unproven safety or efficacy. However, the analysis concluded that there is no legal basis for any preferential waiver, exemption, or tiering strategy for small firms compatible with the public health requirements of the Federal Food, Drug, and Cosmetic Act. Nevertheless, to avoid overlooking any problems or feasible possibilities of relief peculiar to this group of products, the agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC smoking deterrent drug products. Comments regarding the economic impact of this rulemaking should be accompanied by appropriate documentation. The agency previously invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC smoking deterrent drug products. No comments on economic impacts were received.

Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by October 31, 1985. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

The agency has determined that under 21 CFR 25.24(c)(6) (April 26, 1985; 50 FR 16636) that this action is of a type that does not individually or cumulatively have a significant impact on the human environment. Therefore, neither an environmental assessment nor an environmental impact statement is required.

Interested persons may, on or before September 3, 1985 submit to the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before October 31, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before July 3, 1986 may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before September 3, 1986. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA-305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final rule, the agency will ordinarily consider only data submitted prior to the closing of the

administrative record on September 3, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final rule is published in the **Federal Register**, unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 357

OTC drugs, Anthelmintic drug products, Cholecystokinetic drug products, Deodorant drug products for internal use, Orally administered drug products for fever blisters, Poison treatment drug products, Smoking deterrent drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 357 by adding new Subpart G to read as follows:

PART 357—MISCELLANEOUS INTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

* * * * *

Subart G—Smoking Deterrent Drug Products

Sec.

Authority: Secs. 201(p), 502, 505, 701, 52 Stat. 1041–1042 as amended, 1050–1053 as amended, 1055–1056 as amended by 70 Stat. 919 and 72 Stat. 948 (21 U.S.C. 321(p), 352, 355, 371) (5 U.S.C. 553); 21 CFR 5.11.

Subpart G—Smoking Deterrent Drug Products

§ 357.601 Scope.

(a) An over-the-counter smoking deterrent drug product in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each of the conditions in this subpart and each general condition established in § 330.1.

(b) References in this subpart to regulatory sections of the Code of Federal Regulations are to Chapter I of Title 21 unless otherwise noted.

§ 357.603 Definition.

As used in this subpart:

Smoking deterrent. A substance that is used temporarily to help those individuals who want to stop smoking (become cigarette free) or to break the cigarette habit.

§ 357.610 Smoking deterrent active ingredients. [Reserved]

§ 357.650 Labeling of smoking deterrent drugs products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "smoking deterrent."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "A temporary aid to those who want to" (select one or both of the following: "stop smoking cigarettes" or "break the cigarette habit"). Other truthful and nonmisleading statements describing only the indications for use that have been established and listed above, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the prohibitions in section 502(a) of the act against false or misleading labeling and the prohibition in section 301(d) of the act against the introduction into interstate commerce or unapproved new drugs.

(c) *Warnings.* [Reserved]

(d) *Directions.* [Reserved]

Interested persons may, on or before September 3, 1985 submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before October 31, 1985. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before July 3, 1986 may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before September 3, 1986. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final rule, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on September 3, 1986. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final rule is published in the **Federal Register,** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

Dated: February 8, 1985.

Frank E. Young,

Commissioner of Food and Drugs.

Margaret M. Heckler,

Secretary of Health and Human Services.

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