**DEPARTMENT OF HEALTH AND HUMAN SERVICES**

**Food and Drug Administration**

**21 CFR Part 310**

**[Docket No. 81N–0027]**

**RIN 0905–AA06**

## Smoking 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 smoking deterrent drug product for over-the-counter (OTC) human use is not generally recognized as safe and effective and is misbranded. Smoking deterrent drug products are intended to help individuals who want to stop smoking or to break the cigarette habit. 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 smoking 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:** December 1, 1993.

**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, 301–295–8000.

**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 (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 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, after deletion of a small amount of trade secret information, were placed on display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 1–23, 12420 Parklawn Dr., Rockville, MD 20857.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC smoking deterrent drug products was published in the **Federal Register** of July 3, 1985 (50 FR 27552). Interested persons were invited to file by September 3, 1985, written comments, objections, or requests for 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 October 31, 1985. New data could have been submitted until July 3, 1986, and comments on the new data until September 3, 1986. Final agency action occurs with the publication of this final rule on OTC smoking deterrent drug products.

In the **Federal Register** of July 17, 1986 (51 FR 25899), the agency published a notice reopening the administrative record from July 17, 1986 to September 3, 1986 to permit manufacturers to submit, prior to the establishment of a final rule, new data demonstrating the safety and effectiveness of those conditions not classified in Category I (monograph conditions). Interested persons were invited to submit comments on the new data on or before November 3, 1986. Data and information received after the administrative record was reopened are on display in the Dockets Management Branch.

In the preamble to the advance notice of proposed rulemaking on OTC smoking deterrent drug products (47 FR 490), the agency noted that the Panel's report on OTC smoking deterrent drug products did not contain any recommendations for Category I ingredients. However, the Panel proposed Category I labeling in the event that data were submitted that resulted in the upgrading of any ingredients to monograph status prior to the publication of a final rule. The data received by the agency in response to the advance notice of proposed rulemaking were not adequate to support monograph status for any ingredient. Therefore, in the preamble to the proposed rule on OTC smoking deterrent drug products (50 FR 27552 at 27553), the agency stated that in the event that new data submitted to the agency during the allotted 12-month comment and new data period were not sufficient to establish "monograph conditions" for OTC smoking deterrent drug products, the final rule would declare these products to be new drugs. In this final rule, no active ingredient has been determined to be generally recognized as safe and effective in OTC drug products intended for use as a smoking deterrent. Therefore, proposed part 357 (21 CFR part 357), subpart G for OTC smoking deterrent drug products is not being issued as a final regulation.

This final rule declares OTC drug products containing active ingredients for smoking deterrent use 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 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 active ingredients for use as a smoking deterrent by adding new § 310.544 (21 CFR 310.544) to subpart E. The inclusion of OTC smoking deterrent drug products in part 310 is consistent with 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 smoking deterrent drug product, the agency will promulgate an appropriate regulation at that time.

The OTC drug procedural regulations (21 CFR 330.10) 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 Category II or III, the term "nonmonograph conditions" is used.

In the proposed rule for OTC smoking deterrent drug products (50 FR 27552),

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 smoking deterrent drug products to be in compliance with the monograph. Although four manufacturers submitted data and information in response to the proposed rule in an effort to upgrade certain active ingredients, the data and information were not sufficient to support monograph conditions, and no monograph is being established at this time. Therefore, smoking deterrent drug products that are subject to this rule are not generally recognized as safe and effective and are misbranded (nonmonograph conditions). In the advance notice of proposed rulemaking (47 FR 490), the agency stated that the conditions for OTC smoking deterrent drug products that are not generally recognized as safe and effective and are misbranded would be effective 6 months after the date of publication of a final rule in the **Federal Register**. The agency is now adopting the Panel's recommendations that no active ingredient has been determined to be generally recognized as safe and effective for this use. Accordingly, no OTC drug monograph is being established for this class of drug products. Therefore, on or after December 1, 1993, 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. The agency is unaware of any smoking deterrent drug product that is the subject of an approved application. Any such drug product in interstate commerce after the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action.

In response to the proposed rule on OTC smoking deterrent drug products, five manufacturers and one physician submitted comments. No requests were received for oral hearing before the Commissioner of Food and Drugs. 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.

## I. The Agency's Conclusions on the Comments

One comment requested that the definition of a smoking deterrent include reduction in smoking as a viable goal. The comment asserted that epidemiologic studies and empirical research on smoking-related pathology support reduction in smoking as being as valid a goal as cessation of smoking. The comment stated that medical documentation and research (Refs. 1 through 5) have shown that morbidity and mortality are directly related to the amount of cigarettes smoked; therefore, a reduction in smoking is a self-evident beneficial health measure.

In the advance notice of proposed rulemaking for OTC smoking deterrent drug products (47 FR 490 and 492), the Panel stated that "drugs which are purported merely to reduce smoking without the objective of stopping smoking entirely are a waste of the consumer's time and money because of rapid and virtually universal recidivism." Therefore, the Panel concluded that labeling claims of reduction in smoking rather than stopping (cessation) should be Category II (47 FR 496).

In the notice of proposed rulemaking (50 FR 27552 and 27553), the agency stated that recent reports in the literature (Refs. 6, 7, and 8) 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. The agency noted that evidence on the effect of controlled smoking on the health of the individual smoker has been contradictory. Some studies indicated that although smokers may reduce the number of cigarettes smoked or progressively switch to low nicotine-low tar (LN/LT) cigarettes, they inadvertently increase their puff volume, puff frequency, or depth of inhalation and thereby increase smoke-related health risks (Refs. 9 through 12). Other studies suggested 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. 6, 7, 8, 13, 14, and 15). 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. 12). The agency stated that if sufficient evidence becomes available demonstrating that a reduction in smoking results in a significant health benefit to consumers or that reduction in smoking will lead to cessation, 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. Therefore, because of a lack of adequate data, the agency did not include smoking reduction claims in the tentative final monograph. The agency further stated that should sufficient data regarding reduction claims become available before the publication of the final monograph, the agency would consider including reduction in smoking claims in the final monograph. As discussed in comment 2, the only data submitted to support a reduction in smoking claim for OTC smoking deterrent drug products were found to be inadequate. The agency is aware of a recent study by Rennard et al. (Ref. 16) suggesting that short-term smoking reduction may be associated with an improvement in lower respiratory tract inflammation in heavy smokers. However, the authors noted that smokers who reduce smoking compensate for decreased numbers of cigarettes by smoking each more deeply and thoroughly. The authors also stated that caution must be exercised in interpreting the implications of the study. The authors noted that the data do not show unequivocal support for smoking reduction as a therapeutic strategy, but merely show improvement in subclinical lower respiratory tract inflammation. It is not known whether similar inflammatory changes and improvements with smoking reduction could be observed in lighter smokers. Stating that smoking reduction will never be a substitute for cessation, the authors conclude that a prospective double-blind investigation of the long-term results of smoking reduction techniques seems warranted.

Although the epidemiological studies submitted indicate that the effects of smoking are dose-related, i.e., the greater the dose the greater the adverse effect, they do not distinguish between populations with one level of exposure who later adopt another level (heavy or light). Some of the submitted studies have examined the cumulative dose, which is defined as the total number of cigarettes consumed in a lifetime, and its effects on mortality. Generally these studies have shown that the lower the overall dose, the lower the overall risk compared to those smokers who consume larger quantities of cigarettes. However, these epidemiological studies do not show that the reduction in health risks associated with smoking resulted from reduction of smoking alone (lower dose and fewer cigarettes smoked). Rather, the overall reduction results are reported as caused by one or all of

several factors, such as decrease in tar and nicotine content of cigarettes smoked, increase in number of years since smoking cessation, awareness of harmful effects of smoking, cessation of smoking, or a decline in individuals starting to smoke. Therefore, based on these studies, the agency cannot conclude that the health benefits reported result from a reduction in the number of cigarettes smoked per day per individual.

In the 1983 Surgeon General's report on "The Health Consequences of Smoking: Cardiovascular Disease," no evidence was found to suggest that any level of cigarette smoking is safe with regard to coronary heart disease risk (Ref. 17). The report mentions that studies have shown, however, that those who quit cigarette smoking experience a substantial decrease in coronary heart disease mortality and an improvement in life expectancy.

In the 1990 Surgeon General's report on "The Health Benefits of Smoking Cessation," one of the major conclusions was that smoking cessation has major and immediate health benefits for men and women of all ages (Ref. 18). Benefits apply to persons with and without smoking-related disease. No similar data were discussed that related to benefits resulting from reduction of smoking. As the agency stated in the tentative final monograph, as discussed above, if sufficient evidence is provided demonstrating that a reduction in smoking leads to cessation or results in a significant health benefit to consumers, the agency will consider reduction claims for smoking deterrent drug products.

**References**

(1) Cummings, K. M., "Changes in the Smoking Habits of Adults in the United States and Recent Trends in Lung Cancer Mortality," *Cancer Detection and Prevention*, 7:125–134, 1984.

(2) Doll, R., and R. Peto, "Mortality in Relation to Smoking: 20 Years' Observations on Male British Doctors," *British Medical Journal*, 2:1525–1536, 1976.

(3) Kristein, M. M., "40 Years of U.S. Cigarette Smoking and Heart Disease and Cancer Mortality Rates," *Journal of Chronic Disease*, 37(5):317–323, 1984.

(4) Loeb, L.A. et al., "Smoking and Lung Cancer: An Overview," *Cancer Research*, 44:5940–5958, 1984.

(5) Rabkin, S.W., "Effect of Cigarette Smoking Cessation on Risk Factors for Coronary Atherosclerosis. A Control Clinical Trial," *Atherosclerosis*, 53:173–184, 1984.

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

(7) 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.

(8) 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.

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

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

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

(12) "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, 1981.

(13) 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.

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

(15) 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.

(16) Rennard, S.I. et al., "Short-term Smoking Reduction Is Associated With Reduction In Measures of Lower Respiratory Tract Inflammation in Heavy Smokers," *European Respiratory Journal*, 3:752–759, 1990.

(17) "The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General," U.S. Department of Health and Human Services, DHHS Publication No. (PHS) 84–50204, U.S. Government Printing Office, Washington, DC, 1983.

(18) "The Health Benefits of Smoking Cessation. A Report of the Surgeon General," U.S. Department of Health and Human Services, DHHS Publication No. (CDC) 90–8416, U.S. Government Printing Office, Washington, DC, 1990.

2. One comment submitted a number of published articles and studies purporting to show that lobeline sulfate is a safe and effective aid in reducing smoking among those people who wish to do so, in addition to aiding cessation of smoking (Ref. 1).

The studies submitted by the comment in support of lobeline sulfate for a claim of reduction in smoking were previously discussed by the Panel in its report (47 FR 490 at 497) in consideration of lobeline sulfate for a claim of cessation of smoking. (Cessation of smoking was the only claim recognized by the Panel as appropriate for an OTC smoking deterrent drug product.) The Panel concluded that the studies were insufficient to demonstrate effectiveness of the ingredient as a smoking deterrent. The agency agrees with the Panel's assessment. No new studies have been submitted to support cessation claims.

The agency has further reviewed the resubmission of the data for lobeline sulfate submitted in response to the agency's request in the tentative final monograph for data on "reduction" in smoking leading to cessation or lowering the health risks associated with smoking (see comment 1 above). The agency concludes that the data are also insufficient to support a claim of reduction in smoking. The studies measure only short-term reductions, i.e., 3 to 7 days, in the number of cigarettes smoked per day and do not examine long-term reductions, i.e., 4 months to 1 year.

If reduction in smoking claims are to be considered acceptable, criteria similar to those needed to establish "cessation" should be used to establish "reduction" in smoking as a viable goal. The Panel stated that the length of a smoking deterrent study should be at least 4 weeks: 1 week of pretest and at least a 3-week study period (47 FR 490 at 499). Like cessation, for a reduction in smoking claim the agency does not consider it necessary that the drug be taken for 3 weeks. However, an evaluation of effectiveness should take place at least 3 weeks after the drug is started. Although any difference between the drug and placebo for periods shorter than 3 weeks may be statistically significant, the agency does not consider the difference to be clinically significant. Because follow-up data on changes in smoking behavior have indicated that most smokers who reduce their smoking without totally stopping return to baseline smoking levels (Ref. 2), the agency concludes that a study in support of a claim of reduction in smoking must demonstrate long-term reductions in total smoke exposure. It should be noted that, if the only dependent variable to be measured is the "number of cigarettes smoked per unit time," applying data analysis to only this variable may not be sufficient to support a reduction claim because individuals may compensate for changes in nicotine levels (see comment 1 above). For long-term effectiveness, the smoking status of the subjects should be evaluated at the end of 4 months. Recidivism is greatest within 4 months (Ref. 3), and this follow-up period should adequately indicate long-term effectiveness of the treatment.

Thus, based on the short length of time these studies were conducted, the agency concludes that the resubmitted data are inadequate to establish a long-term reduction in total smoke exposure or any significant lowering of health risks that would result in lifetime health benefits from the use of lobeline sulfate for the reduction of smoking. Further, the agency is not aware of any studies on lobeline sulfate that document long-term reductions in the number of cigarettes smoked per day for the majority of smokers.

Because of insufficient data, the agency concludes that these studies are of little value to establish that lobeline sulfate aids reduction or cessation of smoking.

The Panel (47 FR 490 at 497) cited seven other placebo-controlled studies on the effectiveness of lobeline sulfate, all of which it found to be inadequate. The Panel concluded that studies on lobeline sulfate as a smoking deterrent have shown conflicting results and that further testing was necessary to establish effectiveness. The agency agrees that further testing of this ingredient for both "cessation" and "reduction" claims is necessary. The agency points out that publication of this final rule does not preclude a manufacturer's testing an ingredient. However, manufacturers are encouraged to consult with the agency regarding protocols before the initiation of a study. Well-controlled clinical trials conducted generally in accord with the Panel's recommended guidelines (47 FR 498 to 500) and including the types of measurements discussed above would be required to support these claims.

Should adequate data establishing general recognition of safety and effectiveness become available, such data may be submitted in a citizen petition to establish a monograph. (See 21 CFR 10.30 and 330.10(a)(12).) However, marketing of products containing these active ingredients may not continue while the studies are being conducted and the data are being evaluated by the agency.

After the administrative record for this rulemaking had closed, a clinical study protocol was submitted to the agency in support of lobeline sulfate as an OTC smoking deterrent (Ref. 4). The agency has provided comments on this protocol (Ref. 5); however, no study results have been submitted to date. Therefore, at this time, lobeline sulfate is not considered a monograph ingredient in this final rule.

(1) Comment No. C6, Docket No. 81N-0027, Dockets Management Branch.

(2) "The Health Consequences of Smoking: Cardiovascular Disease. A Report of the Surgeon General," U.S. Department of Health and Human Services, DHHS Publication No. (PHS) 84-50204, U.S. Government Printing Office, Washington, DC, 1983.

(3) "Guidelines for Research on the Effectiveness of Smoking Cessation Programs. A Committee Report," National Interagency Council on Smoking and Health, New York, 1974.

(4) Comment No. LET24, Docket No. 81N-0027, Dockets Management Branch.

(5) Letter from W.E. Gilbertson, FDA, to L. Freeman, Pharmaquest Corporation, coded LET30, Docket No. 81N-0027, Dockets Management Branch.

3. Two comments submitted studies in support of the effectiveness of silver acetate and requested its reclassification from Category III to Category I as an OTC smoking deterrent. One comment submitted a double-blind, placebo-controlled clinical study (Refs. 1 and 2), and the second comment submitted an open-label, parallel-group design study (Refs. 3 through 6).

The agency does not find the studies sufficient to support the reclassification of silver acetate from Category III to Category I. In the double-blind, placebo-controlled study, the effectiveness of silver acetate was compared with placebo in 282 subjects who wanted to stop smoking. The study was conducted for 21 days with a 4-month follow-up. On day 21, effectiveness was assessed by chemical means. During the study period, data on the cessation of smoking were obtained by self-reporting and confirmed by blood carboxyhemoglobin levels and urinary nicotine metabolites.

Although the design, methodology, and conduct of the study were sufficient to assess the effect of silver acetate in helping one to stop smoking, the agency finds that in the analysis of the data an inappropriate criterion of "treatment success" was used. The study defined "treatment successes" as those individuals who stopped smoking as measured on the basis of self-reporting, confirmed by blood carboxyhemoglobin levels and urinary nicotine metabolites. Individuals were considered "treatment failures" if they had not stopped smoking by day 18 of the 21-day study. The assessment of the data collected to determine the effectiveness of the drug was, therefore, limited to a 3-day period (days 18 to 21) of the 21-day study. The agency does not consider a 3-day period of abstinence from smoking to be a sufficient predictor of the effectiveness of a drug that is intended to result in smoking cessation. The agency believes that in a study with this objective, subjects should stop smoking within the first 24 to 48 hours after beginning the drug and should be considered "treatment successes" only if they abstain from smoking for the remainder of the study (whether or not the drug is taken the entire time). Even if this criterion were not applied, the results obtained from the study were only marginally significant at best. Fifteen out of a total of 136 subjects in the silver acetate group quit smoking in contrast to 6 out of 146 subjects in the placebo group. This yielded smoking cessation rates of 11 and 4.9 percent for the silver acetate and placebo groups, respectively. The difference between the two groups was statistically significant, $p=0.03$, using a one-tailed t-test. This is not an impressive result because there was a low quit-rate in the placebo group. Further, the study lacked information and details such as case report forms, subject diary cards, and the point at which each subject (drug and placebo) quit smoking during the 3-week study and 4-month follow-up.

The second study was an open-label, parallel-group study comparing the effectiveness of a chewing gum containing 6 milligrams (mg) of silver acetate with a chewing gum containing 2 mg of nicotine alkaloid per piece and an ordinary sugarfree chewing gum (placebo). Subjects were randomized into one of three groups as follows: silver acetate group, 220; nicotine group, 220; and placebo group, 88. These groups were subdivided into groups of 22 subjects each to facilitate group therapy. Each subgroup of 22 was further divided into groups of 4 to 6 subjects to encourage discussion of problems related to smoking cessation. Subjects were evaluated during eight visits over a period of 6 months. During the first five visits, held weekly, the subjects were given group therapy in the form of educational films and lectures. Three additional meetings were held at the end of 6 and 12 weeks and 6 months. At the end of the first visit, subjects were instructed to choose a day to quit smoking. At the sixth visit, subjects were instructed to reduce their chewing gum consumption. The primary efficacy variable was the quit rate (proportion of subjects who had not smoked during the past 6 months since the beginning of the study), based on subject self-reporting and measurements of expired carbon monoxide levels. A follow-up questionnaire was sent to the participants after 1 year to determine their smoking status.

Because of major flaws in design, conduct, and analysis, this study does not meet the requirements of an adequate and well-controlled study. The methods for assessing the subjects' response, as reported in the study results, were not defined in the original

protocol. The protocol did not include a plan for statistical analysis. The inclusion criteria were inadequate because subjects who did not wish to chew gum were permitted to participate in the study. Thus, this allowed subjects who did not chew gum in all treatment groups, which made it hard to differentiate treatment effects. The study was not conducted under blind conditions, and adequate measures were not taken to minimize bias. As acknowledged by the investigators, the placebo group was virtually nonexistent because more than half of the placebo subjects also chewed the nicotine gum (obtained from the market). Further, subjects in all groups chewed placebo gum in addition to or in lieu of their assigned gum. At the end of the study, 15 percent of the subjects using the nicotine gum and placebo gum still used these gums, but only 4 percent of the silver acetate gum group still used this gum.

Because of deficiencies in the presentation of the data and analysis of the study, the statistics for the expired carbon monoxide level (i.e., the primary efficacy variable) cannot be used to verify the reported success rate at the end of 6 months. The data provided consisted of only the means and standard error of the carbon monoxide level of each treatment group at each visit. No individual subject data listings were provided and, thus, no objective measure is available for evaluation which allows for confirmation of smoking cessation. Therefore, the agency cannot confirm the number of subjects who had not smoked during the 6-month study.

The success rates reported at 26 weeks were not statistically significant: nicotine gum 43 percent, silver acetate gum 39 percent, placebo gum 34 percent (Ref. 5). These results are not surprising because a large number of the placebo subjects used the nicotine gum. After several statistical comparisons were made using these data, the investigators' reported results suggested that silver acetate was statistically significantly better than the nicotine gum or placebo for some subgroups. This result indicates that any number of permutations could have been attempted until a particular comparison is significant. However, the multiple comparisons reported in the results, having been made ad hoc, limit the significance of any of the reported findings. Additionally, because there were placebo subjects in the active treatment groups and, thus, no true placebo group existed, the comparisons are a futile exercise.

Because of the deficiencies in the above studies, the agency concludes that further studies are needed to establish the effectiveness of silver acetate as a smoking deterrent drug product ingredient. The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Refs. 7, 8, and 9).

After the administrative record for this rulemaking had closed, two clinical study protocols were submitted to the agency in support of silver acetate as an OTC smoking deterrent (Ref. 10). The agency has provided comments on these protocols (Ref. 11); however, the final results from these studies have not been submitted. Therefore, at this time, silver acetate is not considered a monograph ingredient in this final rule.

**References**

(1) Comment No. C5, Docket No. 81N–0027, Dockets Management Branch.
(2) Comment No. C7, Docket No. 81N–0027, Dockets Management Branch.
(3) Comment No. RPT2, Docket No. 81N–0027, Dockets Management Branch.
(4) Comment No. RPT3, Docket No. 81N–0027, Dockets Management Branch.
(5) Comments No. RPT4 and LET6, Docket No. 81N–0027, Dockets Management Branch.
(6) Comment No. SUP1, Docket No. 81N–0027, Dockets Management Branch.
(7) Letter from W.E. Gilbertson, FDA, to J.Y. Lund, Edgefield Corp., coded LET6, Docket No. 81N–0027, Dockets Management Branch.
(8) Letter from W.E. Gilbertson, FDA, to J.Y. Lund, Edgefield Corp., coded LET10, Docket 81N–0027, Dockets Management Branch.
(9) Letter from W.E. Gilbertson, FDA, to E.T. Sorensen, Fertin Laboratories A/S, coded LET ANS3, Docket No. 81N–0027, Dockets Management Branch.
(10) Comment No. LET22, Docket No. 81N–0027, Dockets Management Branch.
(11) Comment No. LET23, Docket No. 81N–0027, Dockets Management Branch.

## II. The Agency's Final Conclusions on OTC Smoking Deterrent Drug Products

The agency has determined that no active ingredient has been found to be generally recognized as safe and effective and not misbranded as an OTC smoking 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)(19) the following ingredients that had been previously considered under this rulemaking for use as active ingredients in smoking deterrent drug products: clove, coriander, eucalyptus oil, ginger (Jamaica), lemon oil (terpeneless), licorice root extract, menthol, methyl salicylate, quinine ascorbate, silver nitrate, and thymol. The final rule in this document establishes that any smoking deterrent drug product for OTC use is not generally recognized as safe and effective and expands the above-listed nonmonograph ingredients to include all other OTC smoking deterrent active ingredients. These additional ingredients include, but are not limited to, lobeline (in the form of lobeline sulfate or natural lobelia alkaloids or *Lobelia inflata* herb), povidone-silver nitrate, and silver acetate, which were reviewed by the Panel and the agency. Therefore, any ingredient that is labeled, represented, or promoted for use as an OTC smoking deterrent is considered nonmonograph and misbranded under section 502 of the act (21 U.S.C. 352) 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 May 7, 1991 effective date of the final rule mentioned above or the effective date of this final rule that is not in compliance with the regulation is subject to regulatory action.

In order to avoid a duplication in listing smoking deterrent 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 310.544 entitled "drug products containing active ingredients offered over-the-counter (OTC) for use as a smoking deterrent." Accordingly, § 310.545(a)(19) is being removed.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (50 FR 27552 at 27556). 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 the 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 no one of these rules, including this final rule for OTC smoking 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 smoking deterrent drug products is not expected to pose such an impact on small businesses because only a limited number of products are affected. Eleven smoking deterrent ingredients were covered in the earlier final rule that was effective on May 7, 1991. This final rule covers three additional ingredients. Therefore, 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, 706 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, 376); 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. New § 310.544 is added to subpart E to read as follows:

**§ 310.544 Drug products containing active ingredients offered over-the-counter (OTC) for use as a smoking deterrent.**

(a) Any product that bears labeling claims that it "helps stop or reduce the cigarette urge," "helps break the cigarette habit," "helps stop or reduce smoking," or similar claims is a smoking deterrent drug product. Cloves, coriander, eucalyptus oil, ginger (Jamaica), lemon oil (terpeneless), licorice root extract, lobeline (in the form of lobeline sulfate or natural lobelia alkaloids or *Lobelia inflata* herb), menthol, methyl salicylate, povidone-silver nitrate, quinine ascorbate, silver acetate, silver nitrate, and thymol have been present as ingredients in such drug products. There is a lack of adequate data to establish general recognition of the safety and effectiveness of these or any other ingredients for OTC use as a smoking deterrent. Based on evidence currently available, any OTC drug product containing ingredients offered for use as a smoking deterrent cannot be generally recognized as safe and effective.

(b) Any OTC drug product that is labeled, represented, or promoted as a smoking 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 smoking 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 May 7, 1991, any such OTC drug product containing cloves, coriander, eucalyptus oil, ginger (Jamaica), lemon oil (terpeneless), licorice root extract, menthol, methyl salicylate, quinine ascorbate, silver nitrate, and/or thymol initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action. After December 1, 1993, any such OTC drug product containing lobeline (in the form of lobeline sulfate or natural lobelia alkaloids or *Lobelia inflata* herb), povidone-silver nitrate, silver acetate, or any other ingredients 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)(19).

Dated: March 3, 1993.

**Michael R. Taylor,**

*Deputy Commissioner for Policy.*

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