DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 357

[Docket No. 81N-0027]

Smoking Deterrent Drug Products for Over-the-Counter Human Use; Establishment of a Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Advance notice of proposed rulemaking.

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

DATES: Written comments by April 5, 1982, and reply comments by May 5, 1982.

ADDRESS: Written comments to the Dockets Management Branch (formerly the Hearing Clerk's Office) (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Bureau of Drugs (HFD-510), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-443-4960.

SUPPLEMENTARY INFORMATION: In accordance with Part 330 (21 CFR Part 330), FDA received on February 23, 1980 a report of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products on smoking deterrent drug products. FDA regulations (21 CFR 330.10(a)(6)) provide that the agency issue in the **Federal Register** a proposed order containing: (1) The monograph recommended by the Panel, which establishes conditions under which OTC smoking deterrent drug products are generally recognized as safe and effective and not misbranded; (2) a statement of the conditions excluded from the monograph because the Panel determined that they would result in the drugs not being generally recognized as safe and effective or would result in misbranding; (3) a statement of the conditions excluded from the monograph because the Panel determined that the available data are insufficient to classify these conditions under either (1) or (2) above; and (4) the conclusions and recommendations of the Panel. Although the Panel's report on smoking deterrent drug products for OTC use contains no recommendations for Category I ingredients, the Panel is proposing Category I labeling in this document in the event that data are submitted which result in the classification of any smoking deterrent active ingredient into Category I prior to the publication of a final rule.

The unaltered conclusions and recommendations of the Panel are issued to stimulate discussion, evaluation, and comment on the full sweep of the Panel's deliberations. The report has been prepared independently of FDA, and the agency has not yet fully evaluated the report. The Panel's findings appear in this document to obtain public comment before the agency reaches any decision on the Panel's recommendations. This document represents the best scientific judgment of the Panel members, but does not necessarily reflect the agency's position on any particular matter contained in it.

After reviewing all comments submitted in response to this document, FDA will issue in the **Federal Register** a tentative final monograph for OTC smoking deterrent drug products as a notice of proposed rulemaking. Under the OTC drug review procedures, the agency's position and proposal are first stated in the tentative final monograph, which has the status of a proposed rule, final agency action occurs in the final monograph, which has the status of a final rule.

The agency's position on OTC smoking deterrent drug products will be stated initially when the tentative final monograph is published in the **Federal Register** as a notice of proposed rulemaking. In that notice of proposed rulemaking, the agency also will announce its initial determination whether the proposed rule is a major rule under Executive Order 12291 and will consider the requirements of the Regulatory Flexibility Act (5 U.S.C. 601-612). The present notice is referred to as an advance notice of proposed rulemaking to reflect its actual status and to clarify that the requirements of the Executive Order and the Regulatory Flexibility Act will be considered when the notice of proposed rulemaking is published. At that time FDA also will consider whether the proposed rule has a significant impact on the human environment under 21 CFR Part 25 (proposed in the **Federal Register** of December 11, 1979, 44 FR 71742).

The agency invites public comment regarding any impact that this rulemaking would have on OTC smoking deterrent drug products. Types of impact may include, but are not limited to, the following: Increased costs due to relabeling, repackaging, or reformulating; removal of unsafe or ineffective products from the OTC market; and testing, if any. Comments regarding the impact of this rulemaking on OTC smoking deterrent drug products should be accompanied by appropriate documentation.

In accordance with § 330.10(a)(2), the Panel and FDA have held as confidential all information concerning OTC smoking deterrent drug products submitted for consideration by the Panel. All the submitted information will be put on public display in the Dockets Management Branch, Food and Drug Administration, after February 4, 1982, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905 or section 301(j) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 331(j)). Requests for confidentiality should be submitted to William E. Gilbertson, Bureau of Drugs (HFD-510) (address above).

FDA published in the **Federal Register** of September 29, 1981 (46 FR 47730) a final rule revising the OTC procedural regulations to conform to the decision in *Cutler* v. *Kennedy*, 475 F. Supp. 838 (D.D.C. 1979). The Court in *Cutler* held that the OTC drug review regulations (21 CFR 330.10) were unlawful to the extent that they authorized the marketing of Category III drugs after a final monograph had been established. Accordingly, this provision is now deleted from the regulations. The regulations 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," "Category II," and "Category III" at the final monograph stage in favor of 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 because that was the framework in which the Panel conducted its evaluation of the data.

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 6 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 which 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. Further, any OTC drug products subject to this monograph which 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 voluntarily comply with the monograph at the earliest possible date.

A proposed review of the safety, effectiveness, and labeling of all OTC drugs by independent advisory review panels was announced in the **Federal Register** of January 5, 1972 (37 FR 85). The final regulations providing for this OTC drug review under § 330.10 were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). In accordance with these regulations, a request for data and information on all active ingredients used in OTC miscellaneous internal drug products was issued in the **Federal Register** of November 16, 1973 (38 FR 31696). (In making their categorizations with respect to "active" and "inactive" ingredients, the advisory review panels relied on their expertise and understanding of these terms. FDA has defined "active ingredient" in its current good manufacturing practice regulations (§ 210.3(b)(7), (21 CFR 210.3(b)(7))), as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect." An "inactive ingredient" is defined in § 210.3(b)(8) as "any component other than an 'active ingredient.' ") In the **Federal Register** of August 27, 1975 (40 FR 38179) a notice supplemented the initial notice with a detailed, but not necessarily all-inclusive, list of active ingredients in miscellaneous internal drug products to be considered in the OTC drug review. This list, which included smoking deterrent ingredients, was provided to give guidance on the kinds of active ingredients for which data should be submitted. The notices of November 16, 1973, and August 27, 1975, informed OTC drug product manufacturers of their opportunity to submit data to the review at that time and of the applicability of the monographs from the OTC review to all OTC drug products.

Under § 330.10(a) (1) and (5), the Commissioner of Food and Drugs appointed the following Panel to review the information submitted and to prepare a report on the safety, effectiveness, and labeling of the active ingredients in these OTC miscellaneous internal drug products:

Diana F. Rodriguez-Calvert, Pharm. D. (appointed July 1976), Acting Chairman.
John W. Norcross, M.D., Chairman (resigned March 1979).
Ruth Eleanor Brown, R.Ph. (resigned May 1976).
Elizabeth C. Giblin, M.N., Ed. D.
Richard D. Harshfield, M.D.
Theodore L. Hyde, M.D.
Claus A. Rohweder, D.O. (deceased April 13, 1979).
Samuel O. Thier, M.D. (resigned November 1975).
William R. Arrowsmith, M.D. (appointed March 1976).

Representatives of consumer and industry interests served as nonvoting members of the Panel. Eileen Hoates, nominated by the Consumer Federation of America, served as the consumer liaison until September 1975, followed by Michael Schulman, J.D. Francis J. Hailey, M.D., served as the industry liaison, and in his absence John Parker, Pharm. D., served. Dr. Hailey served until June 1975, followed by James M. Holbert, Sr., Ph. D. All industry liaison members were nominated by the Proprietary Association.

The following FDA employees assisted the Panel: Armond M. Welch, R.Ph., served as the Panel Administrator until July 1979, followed by John R. Short, R.Ph. Enrique Fefer, Ph. D., served as the Executive Secretary until July 1976, followed by George W. James, Ph. D., until October 1976, followed by Natalia Morgenstern until May 1977, followed by Arthur Auer until October 1978. Roger Gregorio served as the liaison for the Office of New Drug Evaluation beginning November 1978. Joseph Hussion, R.Ph., served as the Drug Information Analyst until July 1976, followed by Anne Eggers, R.Ph., M.S., until October 1977, followed by John R. Short, R.Ph., until July 1979.

In order to expand its scientific base, the Panel called upon the following consultants for advice in areas which required particular expertise:

Lynn R. Brady, Ph. D. (pharmacognosy).
Arthur E. Schwarting, Ph.D. (pharmacognosy).
Ralph B. D'Agostino, Ph. D. (statistics).

The Advisory Review Panel on OTC Miscellaneous Internal Drug Products was charged with the review of many categories of drugs, but due to the large number of ingredients and varied labeling claims, the Panel decided to review and publish its findings separately for several drug categories and individual drug products. The Panel presents its conclusions and recommendations for smoking deterrent drug products in this document. The review of all other categories of miscellaneous internal drug products is being continued by the Panel, and its findings are being published periodically in the **Federal Register**.

The Panel was first convened on January 13, 1975 in an organizational meeting. Meetings at which smoking deterrent drug products were discussed were held on the following dates: March 2 and 3, April 17 and 18, June 2 and 3, September 29 and 30, December 8 and 9, 1979, and February 23 and 24, 1980.

The minutes of the Panel meetings are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration (address above).

Donald J. Flaster, M.D., was given an opportunity to appear before the Panel to express his views on smoking deterrent drug products at his own request.

No person who so requested was denied an opportunity to appear before the Panel to discuss smoking deterrent drug products.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from an interested person, and has considered all pertinent data and information submitted through February 23, 1980 in arriving at its conclusions and recommendations for OTC smoking deterrent drug products.

In accordance with the OTC drug review regulations in § 330.10, the Panel reviewed smoking deterrent drug products with respect to the following three categories:

Category I. Conditions under which OTC smoking deterrent drug products are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC smoking deterrent drug products are not generally recognized as safe and effective or are misbranded.

Category III. Conditions for which the available data are insuficient to permit final classification at this time.

The Panel reviewed 45 smoking deterrent active ingredients and classified no ingredients in Category I, 43 ingredientas in Category II, and 2 ingredients in Category III.

I. Submission of Data and Information

Pursuant to the notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179) requesting the submission of data and information on OTC miscellaneous internal drug products, the following firms made submissions related to products used as smoking deterrents:

A. Submissions by Firms.

Firms and Products

Anti-Tobacco Information Center, Inc., Rouses Point, NY 12979—Nicocortyl tablets.

Campana Corp., Batavia, IL 60510—Bantron tablets.

S.A. Cravotta Co., Arlington, VA 22201—I Quit spray.

Edgefield Corp., Convent, NJ 07961—Tabmint chewing gum.

Health Sciences Associates, Inc., Bethesda, MD 20014—Nicoprive tablets.

B. Ingredients Reviewed by the Panel

1. *Labeled ingredients contained in products submitted to the Panel.*

Alcohol
Ammonium chloride
Calcium phosphate, tribasic
Cloves, ground
Co-carboxylase
Coriander, ground
Cornstarch
Eucalyptus oil
Ginger, ground Jamaica
Gum arabic, powdered
Hawthorne, dry alcoholic extract of
Lactose
Lemon oil, terpeneless
Licorice root extract
Lobelia alkaloids, natural
Magnesium carbonate
Magnesium stearate
Menthol
Methyl salicylate
Nicotinic acid
Pyridoxine hydrochlorate
Quinine ascorbate
Silver acetate
Sodium ascorbate
Sugar
Talc
Thiamine mononitrate
Thymol

2. *Other ingredients.* In addition to those ingredients included in the products submitted to the Panel, the Panel reveiwed the following ingredients which were listed in the **Federal Register** notice of August 27, 1975 (40 FR 38179).

Aloin
Aluminium hydroxide
Belladonna leaves, extract of
Benzocaine
Capsicum
Cascara sagrada, extract of
Chlorophyllins
Cimicifuga
Gentain, solid extract of
Lobelia
Lobeline sulfate
Methapyrilene hydrochloride
Nux vomica, extract of
Potassium gentian root
Potassium nux vomica
Propylene glycol
Silver nitrate
Sodium chloride

C. Classification of Ingredients

1. *Active ingredients.*

Cloves, ground
Coriander, ground
Eucalyptus oil
Ginger, ground Jamaica
Lemon oil, terpeneless
Licorice root extract
Lobeline (in the form of the lobeline sulfate or its pharmacological equivalent as natural lobelia alkaloids or *obelia inflata* herb)
Menthol
Methyl salicylate
Quinine ascorbate
Silver acetate
Thymol

2. *Other ingredients.* The Panel was neither able to locate nor is it aware of any significant body of data demonstrating the safety and effectiveness of the following OTC ingredients when used as smoking deterrents. The Panel, therefore, classifies these ingredients as Category II for this use, and they will not be reviewed further in this document.

Alcohol
Aloin
Aluminium hydroxide
Ammonium chloride
Belladonna leaves, extract of
Benzocaine
Capsicum
Cascara sagrada, extract of
Chlorophyllins
Cimicifuga
Co-carboxylase
Cornstarch
Gentian, solid extract of
Gum arabic, powdered
Hawthorne, dry alcoholic extract of
Lactose
Magnesium strearate
Methapyrilene hydrochloride
Nicotinic acid
Nux vomica, extract of
Potassium gentian root
Potassium nux vomica
Propylene glycol
Pyridoxine hydrochlorate
Silver nitrate
Sodium ascorbate
Sodium chloride
Sugar
Talc
Thiamine mononitrate

3. *Adjuvants.* These are ingredients incorporated in drug products which may aid in the action of the active ingredient. The possible role of these ingredients is discussed below. (See part III. paragraph C.1.a. below—Lobeline.)

Calcium phosphate, tribasic
Magnesium carbonate

D. Referenced OTC Volumes

The "OTC Volumes" cited throughout this document include submissions made by interested persons in response to the call-for-data notices published in the **Federal Register** of November 16, 1973 (38 FR 31696) and August 27, 1975 (40 FR 38179). All of the information included in these volumes, except for those deletions which are made in accordance with the confidentiality provisions set forth in § 330.10(a)(2), will be put on public display after February 4, 1982, in the Dockets Management Branch (HFA–305), Food and Drug Administration, Room 4–62, 5600 Fishers Lane, Rockville, MD 20857.

II. General Statements and Recommendations

A. Definitions of Terms

For the purposes of this document the Panel has agreed on the following definitions:

1. *Heavy smokers.* Those persons who smoke at least 20 cigarettes per day.

2. *Long-term, chronic smokers.* Those persons who have smoked cigarettes regularly for at least 5 years.

3. *Recidivism.* Return to previous cigarette smoking pattern.

4. *Smoking deterrent.* A substance which helps one to stop smoking cigarettes.

B. General Discussion

Products have been submitted to the Advisory review Panel on OTC Miscellaneous Internal Drug Products bearing labeling claims "to stop smoking" or "to reduce smoking." However, this document deals solely with OTC smoking deterrent drug products which help one to stop smoking cigarettes. Smoking deterrent drug products, in general, either alter the tobacco taste so that smoking becomes less pleasant to the smoker or substitute a nicotine-like drug in an oral dosage form in an amount sufficient to produce a pharmacological effect that alters the smoker's habit or addiction. The Panel believes 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. The Panel believes

that the willpower and motivation of the consumer are essential for the action of products designed to help the individual reduce or stop smoking.

After tobacco was introduced in Europe by the 16th century explorers returning from North America, its use and cultivation rapidly spread throughout the world (Ref. *1*). In 1623, Sir Francis Bacon observed that "the use of tobacco is growing greatly; it conquers men with a certain secret pleasure so that those who have once become accustomed thereto can hardly be restrained therefrom" (Ref. *1*). Three hundred and fifty-seven years later, the Panel finds no reason to dispute this statement.

Over the years substances such as corn silk, coffee grounds, and dried lettuce leaves have been substituted as smoking material with little acceptance. This leads to the conclusion that there is indeed something in tobacco which imparts a "certain secret pleasure." Of the various substances in tobacco (nicotine, pyridine and other nitrogenous bases, a family of isoprenoid compounds, volatile acids, tarry and phenolic substances, furfural, and acrolein), nicotine, which is believed to have addictive or habit forming properties, is known to exert a strong stimulating effect on the central nervous system and a peripheral stimulating effect on the autonomic nervous system (Ref. *2*).

Attempts by confirmed smokers to stop smoking are as numerous as are the different methods used. There is little evidence supporting a long-term success rate of significant proportion in modifying smoking behavior, whether or not oral medications (tranquilizers, stimulants, or nicotine substitutes) are used, with or without various psychological techniques. Short-term success rates are often found with all techniques. The high rate of resumption of smoking after a period of abstinence is influenced by many factors (personality, psychosocial stress, etc.). These factors are clearly unrelated to the effectiveness of the drug whose purpose is to help the individual break the smoking habit. The responsibility of this Panel is to evaluate only the effectiveness of the drug in helping the person to break the habit.

Since 1969, 29 million smokers have quit smoking, and it is estimated that 95 percent have done so without counseling or a structured program as indicated in the Surgeon General's report on "Smoking and Health" (Ref. *3*). Also it is known that among smokers experiencing a first myocardial infarction, 30 to 50 percent will stop permanently upon minimal advice of a physician. The characteristics of these groups have been little explored.

Some techniques used to help a smoker reduce or stop smoking have been reviewed by the Surgeon General (Ref. *3*) and are briefly summarized by this Panel:

(1) Counseling programs consisting of individual or group therapy have produced 1-year abstinence rates of 13 to 30 percent.

(2) Educational campaigns have reduced cigarette consumption by 20 to 30 percent below its predicted 1975 level.

(3) Proprietary or public service clinics have produced good immediate abstinence rates with approximately 30 percent reporting abstinence at 1 year.

(4) Fifteen to twenty percent of subjects highly susceptible to hypnosis can be expected to have a long-term abstinence from smoking through this technique.

(5) Sensory deprivation techniques have produced a long-term success rate of up to 27 percent in small numbers of subjects.

(6) Behavior modification has had a long-term success rate of approximately 25 percent.

(7) Aversion techniques such as satiation and rapid smoking have been reported to have up to 60 percent of subjects abstinent at 6 months in a few studies. However, these techniques present a considerable cardiovascular risk because of increased nicotine and carbon monoxide in the body. Aversion to smoking through electric shocks has been reported to have a success rate of 80 percent in small numbers of subjects in combination with other treatment methods.

Interpretation of results in many studies involving a change in smoking behavior is difficult because of differences or defects in study design. Many studies have been uncontrolled or poorly controlled, and few have used long-term followups with objective measurements. It also has been impossible to differentiate between "long-term" and "1-year" abstinence. Most reports have been based on unverified self-reporting of the number of cigarettes smoked during a period. Objective methods to measure smoking behavior such as measuring blood levels of nicotine, cotinine (a major metabolite of nicotine), carbon monoxide, and thiocyanate must be included in studies recommended by this Panel because false reporting by persons trying to stop smoking has been confirmed by such methods in several programs involving smoking modification.

Within 5 minutes after smoking, blood levels of nicotine peak and about half of this amount of nicotine is excreted in 30 minutes. Plateau levels are reached in 2 to 3 hours by chronic smokers and the blood is cleared in approximately the same time when smoking is stopped (Ref. *4*). Excretion of nicotine in the urine varies greatly with changes in the urine pH (an acidic urine increases excretion). Urine will be free of nicotine within 12 hours after the individual has stopped smoking. Therefore, blood or urine measurements of nicotine would only confirm that the subject has smoked within the last several hours.

Cotinine, the major metabolite of nicotine, has about one-fiftieth the pharmacologic activity of nicotine. Fifty percent excretion of cotinine occurs in about 30 hours so the presence of cotinine in the blood would indicate that the subject has smoked within the last 5 to 7 days (Ref. *5*).

Carbon monoxide in expired air of smokers is easily and relatively inexpensively measured, and its presence indicates smoking activity within a period of about 12 hours; however, its presence is modified by environmental factors, e.g., living in an area where normal levels of carbon monoxide in the air are higher than average. Therefore, this measurement is not a reliable indication of cigarette smoking activity.

Blood thiocyanate levels indicate exposure to hydrocyanic acid which is present in cigarette smoke in small amounts. Elevated levels are present for approximately 1 month after smoking is stopped. Since certain foods, such as cabbage and brussel sprouts, also cause increased blood levels of thiocyanate, thiocyanate levels by themselves are unreliable as indicators of smoking behavior. A combination of elevated carbon monoxide in expired air and elevated thiocyanate levels is considered proof of smoking activity (Ref. *6*).

The Panel recognizes that a high percentage of recidivism is likely to occur within the first 4 months after stopping smoking (Ref. *7*). The Panel also recognizes that recidivism may occur after stopping smoking for a short time, but the Panel believes that the most difficult time period for an individual to stop smoking is the first few weeks. Although this time is variable, the Panel has selected a period of 3 weeks in order to evaluate the effectiveness of smoking deterrents.

References

(*1*) Brecher, E. M., "Licit and Illicit Drugs," Little, Brown and Co., Boston, p. 209, 1972.

(*2*) Bolle, R. L., and G. D. Koelle, "Ganglionic Stimulating and Blocking Agents," *in* "The Pharmacological Basis of

Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, pp. 567–568, 1975.

(3) "Smoking and Health. A Report of the Suregeon General," U.S. Department of Health, Education, and Welfare, DHEW Publication No. (PHS) 79–50066, 1979.

(4) Isaac, P. F., and M. J. Rand, "Cigarette Smoking and Plasma Levels of Nicotine," *Nature*, 236:308–310, 1972.

(5) Zeidenberg, P., et al., "Nicotine: Cotinine Levels in Blood During Cessation of Smoking," *Comprehensive Psychiatry*, 18:93–101, 1977.

(6) Vogt, T. M., et al., "Expired Air Carbon Monoxide and Serum Thiocyanate as Objective Measures of Cigarette Exposure," *American Journal of Public Health*, 67:545–549, 1977.

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

C. Labeling

The Panel has carefully reviewed the submitted labeling claims for products promoted as smoking deterrents and has classified them as Category I or Category II. The Panel did not identify any Category III labeling. The Panel realizes that other terms may be developed to express the same Category I indications. However, only those indications and warnings listed under Category I are generally recognized to be acceptable at this time.

In order for any labeling to be acceptable, it must include (1) the indication(s) for use, (2) pertinent warnings and contraindications, and (3) clear directions for use that include the recommended dosage.

The Panel believes that all labeling should be clear, concise, easily read, and understood by most consumers. It has followed this concept in the development of all Category I labeling. The Panel is also concerned about the size and color of the print used in labeling of these and all OTC drug products, and recommends that manufacturers make an effort to design legible labeling.

One of the primary functions of this Panel is to attempt to eliminate confusing labeling claims. Some of the labeling on currently marketed smoking deterrent drug products is unsupported by scientific data and in some cases misleading. The Panel believes that if two ingredients are indistinguishable with regard to effectiveness, it is misleading to claim superiority for one. Accordingly, such labeling has been placed in Category II.

The indications for use should be simply and clearly stated; the directions for use should provide the user with enough information for safe and effective use of the product.

Undocumented or misleading claims such as "does not require any willpower" and colloquial or provincial expressions that have no meaning to most people must not be used. In the labeling, effectiveness shall not be related to the physical characteristics of the product, except as those characteristics may relate to the action of the active ingredients.

The Panel believes that the pharmacological effect of the drug being studied is only temporary and by itself is not sufficient to cause long-term stopping of smoking which instead must result from the smoker's willingness and motivation to refrain from smoking after the use of the drug product is stopped. The Panel believes that claims for long-term effectiveness of the drug are misleading unless documented by studies of adequate duration.

The Panel is aware of the current OTC labeling regulation dealing with warning statements (21 CFR 330.1(g). The Panel concurs with the warning, "Keep this and all drugs out of the reach of children," and believes that it should be incorporated in the smoking deterrent labeling. However, the Panel recommends that the other warning statement required by § 330.1(g) ("In case of accidential overdose, seek professional assistance or contact a Poison Control Center immediately") be revised to read as follows: "In case of accidential overdose, contact a Poison Control Center, Emergency Medical Facility, or Physician immediately for advice." The Panel believes that this revision will be more informative to the consumer.

Because OTC products can be purchased by anyone, it is the view of the Panel that the public generally does not regard them as products which can result in injurious or potentially serious consequences if improperly used. The public needs to be continually alerted to the idea that these products, like all medicine, carry some risk and should be used with caution. The consumer should also be informed of signs or symptoms of known toxicity requiring use of the drug to be discontinued.

In addition, the Panel recommends that the drug product labeling contain instructions for the most effective use of the product. These instructions should be displayed prominently on all package labeling.

The Panel recommends that the label should contain a listing of all ingredients, clearly indicating which are active and which are inactive. Active ingredients should be listed by their established names, and the label should state the quantity of the active ingredient included in a single dose.

D. Combination Policy

The Panel agrees with FDA's general combination policy as stated in § 330.10(a)(4)(iv) (21 CFR 330.10(a)(4)(iv)) and with the agency's "General Guidelines for OTC Drug Combination Products" for which the notice of availability was published in the **Federal Register** of November 28, 1978 (43 FR 55466). As they apply to the combination smoking deterrent drug products reviewed in this document, the following two sections are particularly appropriate in the Panel's view:

1. The portion of regulation § 330.10(a)(iv) which states,

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each ingredient makes a contribution to the claimed effect(s); * * *, and

2. The portion of FDA's "General Guidelines for OTC Drug Combination Products" which states,

> Category I active ingredients from the same therapeutic category that have the same mechanism of action should not ordinarily be combined unless there is some advantage over the single ingredients in terms of enhanced effectiveness, safety, patient acceptance, or quality of formulation. They may be combined in selected circumstances to treat the same symptoms or conditions if the combination meets the OTC combination policy in all respects, the combination offers some advantage over the active ingredients used alone, and the combination is, on a benefit-risk basis, equal to or better than each of the active ingriendients used alone at its therapeutic dose.

III. Smoking Deterrent Drug Products

A. Category I Conditions

The following are Category I conditions under which smoking deterrent drug products are generally recognized as safe and effective and are not misbranded.

1. *Category I active ingredients.* None.

2. *Category I labeling.* Although the Panel has not classified any ingredients in Category I, it recommends the following Category I labeling for smoking deterrent drug products which contain ingredients found to be generally recognized as safe and effective and not misbranded, as well as any specific labeling discussed in the individual ingredient statements.

a. *Indications.* The product labeling should contain one or more of the following statements:

(1) "A temporary aid to those who want to stop smoking cigarettes."

(2) "Helps you stop the cigarette urge temporarily."

(3) "Helps you stop smoking cigarettes temporarily."

(4) " A temporary aid to breaking the cigarette habit."

b. *Other required statement.* All product labeling must contain the following statement: "This product's effectiveness is directly related to the user's motivation to stop smoking cigarettes."

Other allowable statement. In addition to the above required labeling, the Panel will allow product labeling to contain a descrition (in lay language) of the specifc proven mechanism of action of the active ingredients under the heading "Mechanism of Action."

B. Category II Conditions

The following are Category II conditions under which smoking deterrent drug products are not generally recognized as safe and effective or are misbranded.

1. *Category II active ingredient—Quinine ascorbate.* Quinine ascorbate was submitted to the Panel as part of a product which also contains vitamins and a dry alcoholic extract of hawthorne. The submission to the Panel did not identify the active ingredient(s). However, the Panel assumes that the quinine ascorbate is the intended active ingredient and concludes that it is safe in the dose noted below, but is not generally recognized as an effective smoking deterrent.

(1) *Safety.* The Panel found quinine ascorbate to be discussed only in the Merck Index (Ref. *1*), and only as a chemical. No discussion of any pharmacological action could be found other than as quinine. The usual daily dose of quinine (calculated as the sulfate salt) is 650 milligrams (mg) every 8 hours which greatly exceeds the manufacturer's suggested daily dose for quinine ascorbate of 8 mg taken 8 times a day as a smoking deterrent (Ref. *2*).

Ascorbic acid (vitamin C), and ascorbate salts (ascorbyl palmitate, calcium ascorbate, niacinamide ascorbate, and sodium ascorbate), were reviewed by the Advisory Review Panel on OTC Vitamin, Mineral, and Hematinic Drug Products and its conclusions were published in the **Federal Register** of March 16, 1979 (44 FR 16126). That Panel found that doses of vitamin C in excess of 1 gram (g) may produce increased excretion of oxalate, uric acid, and calcium, which in turn may enhance the risk of crystal formation in the kidney and bladder (44 FR 16140). But that Panel concluded that a maximum safe daily dose is 500 mg (44 FR 16141), which greatly exceeds the possible dose from quinine ascorbate used as a smoking deterrent.

Ascorbic acid and ascorbate salts are common articles of the diet and are sometimes consumed in large doses by the American public. The Panel, therefore, considers that quinine ascorbate is safe when used at a dose of 8 mg taken eight times daily as a smoking deterrent.

Since quinine is generally recognized as safe and since ascorbic acid and ascorbate salts are generally recognized as safe, the Panel concludes that quinine ascorbate is generally recognized as safe for OTC use as a smoking deterrent.

(2) *Effectiveness.* The effectiveness of quinine ascorbate as a smoking deterrent is not substantiated in the submission (Ref. *2*). Reference to its use as a smoking deterrent could not be found in any scientific literature, and no references to such literature were included in the submission. There is no indication from the clinical results reported that the "studies" are any more than testimonials and are not compatible with recognized standards of adequate and well-controlled clinical investigations. Quinine ascorbate was incorporated in a clinical study submitted by another firm (Ref. *3*); however, due to limited conclusions that could be drawn from the statistical analysis, its efficacy in that study could not be determined. (See part III. paragraph B.2.a. below—Licorice root extract, ground coriander, ground ginger (Jamaica), ground cloves, lemon oil (terpeneless), and orange oil.) Furthermore, the Panel is not aware of quinine ascorbate ever being marketed in this country as a smoking deterrent. Therefore, the Panel concludes that quinine ascorbate is not generally recognized as an effective smoking deterrent.

(3) *Evaluation.* The Panel concludes that quinine ascorbate is generally recognized as safe, but it is not generally recognized as an effective smoking deterrent.

The combination product containing this ingredient has never been marketed in the United States. The Panel considers the entire combination irrational since no effectiveness has been demonstrated for the quinine ascorbate, the vitamins most likely would have no effect as a smoking deterrent, and the Panel has not been able to find any reference to the use of hawthorne extract as a smoking deterrent.

References

(*1*) "Merck Index," 9th Ed., Merck and Co., Inc., Rahway, NJ, p. 1048, 1976.

(*2*) OTC Volume 170001.

(*3*) OTC Volume 170169.

2. *Category II combinations.*

Licorice root extract, ground coriander, ground ginger (Jamaica), ground cloves, lemon oil (terpeneless), and orange oil

Methyl salicylate, eucalyptus oil, menthol, and thymol.

a. *Licorice root extract, ground coriander, ground ginger (Jamaica), ground cloves, lemon oil (terpeneless), and orange oil.* The Panel concludes that a combination of these spices and flavors is safe for OTC use in the doses noted below, but it is not generally recognized as an effective smoking deterrent.

(1) *Safety.* These common spices and essential oils are generally recognized as safe for human use as food additives in §§ 182.10 and 182.20 (21 CFR 182.10 and 182.20). The Panel realizes that the concentration of the ingredients in this type of formulation will be greater than that used as a food additive. This would be necessary in order for the product to achieve its intended purpose of overwhelming the gustatory and olfactory senses. The Panel believes that the margin of safety of these ingredients is wide enough so that quantities in excess of those used as food flavors may be safely used in smoking deterrent drug products.

In review of the formulation submitted to the Panel as a smoking deterrent, the Panel does not consider the concentration of any of the ingredients to pose a safety problem when used as a smoking deterrent and, therefore, concludes that the entire formulation is generally recognized as safe for OTC use as a smoking deterrent.

(2) *Effectiveness.* The recommended use for this combination of spices and essential oils involves sucking on a tablet whenever there is a desire to smoke. These ingredients are claimed to act as physiological satisfiers of the gustatory and olfactory senses by overwhelming them while simultaneously satisfying the physical sensation of oral gratification.

Only one clinical study (Ref. *1*) was submitted to the Panel, and the Panel is not aware of any others. This study involves the comparative testing of the spice and essential oil formulation (Formula I) and a quinine ascorbate formulation (Formula II) as smoking deterrents. All subjects received "support therapy" which included medical supervision and medications for other conditions as necessary. Seventy-four individuals were assigned to one of three drug therapy groups as follows:

(1) Formula I plus support therapy (41 individuals),

(2) Formula II plus support therapy (19 individuals), and

(3) Formula I and Formula II plus support therapy (14 individuals).

Results of the study show that 30 (73.2 percent) of the individuals in group (1) reduced their cigarette consumption by more than 50 percent, along with 13 (68.4 percent) in group (2), and 9 (64.3 percent) in group (3). The numbers and percentages for those who stopped smoking in each group are 10 (24.4 percent), 3 (21.1 percent), and 3 (21.4 percent), respectively.

The Panel found several problems with this study. The study was neither placebo-controlled nor double-blind. Subjects were not randomly assigned to groups. Support therapy was provided for each group. Because of these problems, conclusions drawn from any statistical analysis of the study are extremely limited. It is appropriate to conclude that with regard to reduction (by more than 50 percent) and stopping of smoking there are no statistically significant differences among the 3 groups. However, the Panel was unable to provide any conclusions or statements on the effectiveness of the spice and essential oil formulation (or any of the other drug groups) because there was no information which allowed the Panel to differentiate between the effects of the drug(s) and the effects of the support therapy.

(3) *Evaluation.* The Panel concludes that the combination of spices and essential oils mentioned above is generally recognized as safe for OTC use when used in doses intended as a smoking deterrent, but it is not generally recognized as an effective smoking deterrent.

Reference

(1) OTC Volume 170169.

b. *Methyl salicylate, eucalyptus oil, menthol, and thymol.* The Panel concludes that a combination of methyl salicylate, eucalyptus oil, menthol, and thymol is safe for OTC use in doses used as a smoking deterrent, but is not generally recognized as an effective smoking deterrent.

(1) *Safety.* Eucalyptus oil, menthol, methyl salicylate, and thyme oil (contains 20 to 30 percent thymol) have been classified by the National Academy of Sciences (Ref. *1*) as flavoring agents for foods. In addition, eucalyptol (eucalyptus oil contains not less than 70 percent of eucalyptol), menthol, and thymol are permitted by FDA as food additives (synthetic flavoring substances) when used in the minimum quantities required to produce their intended effect (21 CFR 172.515).

Since methyl salicylate is the only one of these four ingredients not specifically permitted as a food additive by FDA regulations, the Panel felt obligated to review its toxicity. Methyl salicylate toxicity is similar to that of other salicylate preparations, such as aspirin and sodium salicylate. The minimum lethal dose for children is 4 milliliters (mL) (Ref. *2*). The fact that it is a liquid with a pleasant aroma makes it very attractive and increases its potential for consumption by children.

Davison et al. (Ref. *3*) were able to demonstrate that methyl salicylate is quickly hydrolyzed to free salicylate in animals and man and therefore concluded that toxicity is due to free salicylate and not to the unhydrolyzed methyl ester (methyl salicylate). Results of their study show negligible plasma levels of methyl salicylate in dogs and rats 60 minutes after administration, whereas 21 percent of the total salicylate in human plasma was still present as methyl salicylate after 90 minutes. This more rapid hydrolysis of methyl salicylate in animals (dogs and rats) probably explains the greater toxicity of methyl salicylate in these animals as compared to humans and substantiates the conclusion that methyl salicylate toxicity is due to free salicylate.

In review of the formulation submitted (Ref. *4*) to the Panel as a smoking deterrent, the toxicity of the methyl salicylate component is not considered to be a risk because of the small amount included. Therefore, the product itself is generally recognized as safe for its intended OTC use as a smoking deterrent.

(2) *Effectiveness.* No clinical studies were submitted for this combination of ingredients, and the Panel was unable to find any reference to clinical studies in the literature since this combination of ingredients has not been marketed in the United States as a smoking deterrent. There were merely a few testimonials in the material submitted to the Panel (Ref. *4*). The Panel concludes that a combination of methyl salicylate, eucalyptus oil, menthol, and thymol is not generally recognized as an effective smoking deterent.

(3) *Evaluation* The Panel concludes that a combination of methyl salicylate, eucalyptus oil, menthol, and thymol is generally recognized as safe for OTC use when used in doses intended as a smoking deterrent, but it is not generally recognized as an effective smoking deterrent.

References

(*1*) "Food Chemicals Codex." 2d Ed., Committee on Specifications of the Committee on Food Protection, National Research Council, National Academy of Sciences, Washington, 1972.

(*2*) Woodbury, D. M., and E. Fingl, "Analgesic-Antipyretics Anti-inflammatory Agents, and Drugs Employed in the Therapoy of Gout," *in* "The Pharmacological Basis of Therapeutics," 5th Ed., edited by L. S. Goodman and A. Gilman, The MacMillan Co., New York, p. 336, 1975.

(*3*) Davison, C., et al., "On the Metabolism and Toxicity of Methyl Salicylate," *Journal of Pharmacology and Experimental Therapeutics*, 132:207–211, 1961.

(*4*) OTC Volume 170168.

3. *Category II labeling.* The Panel concludes that the following labeling claims are either unsupported by scientific data or are misleading. Claims of reduction in smoking rather than stopping are included in this list because the Panel does not consider reduction a satisfactory achievement due to rapid and virtually universal recidivism. The claims listed below and other related terms are classified as Category II labeling for smoking deterrent drug products:

a. "A tempoorary aid to cut down on smoking."

b. "An aid to those who want to reduce the smoking habit."

c. "Curbs the tobacco urge."

d. "Helps to stop smoking without requiring will power."

C. Category III Conditions.

The following are Category III conditions for which the available data are insufficient to permit final classification at this time.

1. *Category III active ingredients.*

Lobeline (in the form of lobeline sulfate or its pharmacological equivalent as natural lobelia alkaloids or *Lobelia inflata* herb).

Silver acetate.

a. *Lobeline (in the form of lobeline sulfate or its pharmacological equivalent as natural lobelia alkaloids or* Lobelia inflata *erb*). The Panel concludes that lobeline sulfate is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness as a smoking deterrent.

(1) *Safety.* Lobeline is an alkaloid obtained from *Lobelia inflata.* Lobeline is normally employed as the sulfate salt, but the less purified forms of the ingredient, i.e., natural lobelia alkaloids or *Lobelia inflata* herb, may be used in amounts that contain pharmacologically equivalent amounts of lobeline. The neuropharmacologic actions of lobeline are similar to those of nicotine but much weaker, and its principal effects are considered to be due to its action on the

autonomic ganglia, vomiting center, and respiratory center (Ref. *1*). From a single dose of 8 mg lobeline sulfate the most frequent symptoms reported (Ref. *1*) include gaseous eructations (belching), epigastric pain (stomach ache), severe heartburn, nausea, vomiting, and faintness. Few symptoms have been reported following doses of 2 mg three times a day. Rapp (Ref. *2*) found no significant changes in blood pressure, pulse, or respiration during a 10-day treatment using 6 mg lobeline sulfate (2 mg three times daily), when given in combination with antacids, in 23 healthy subjects between the ages of 17 and 43.

Rapp, Dusza, and Blanchet (Ref. *3*) claimed that tribaasic calcium phosphate and magnesium carbonate in doses of 130 mg each served as antacid adjuvants to increase the absorption of 2 mg lobeline sulfate and enhance the blood levels. To date this has not been independently confirmed. A single dose (2 mg) of the buffered product was found to have no more effect on blood pressure, pulse, respiratory rate, digital skin temperature, or gastric symptoms than a starch placebo (Ref. *4*). Studies designed to demonstrate effectiveness have not reported any evidence of clinical toxicity resulting from up to 6 weeks of use (Refs. *3* through *14*). No chronic toxicity studies have been made available to the Panel.

The Panel, therefore, concludes that lobeline sulfate is safe for OTC use at a dose of 2 mg up to three times a day for no longer than 6 weeks. Any claim for longer use would require chronic toxicity studies.

(2) *Effectiveness.* Although Rapp, Dusza, and Blanchet (Ref. *3*) found that the blood level of lobeline sulfate, when given in combination with antacids, was directly related to success in curbing smoking in 28 smokers who wanted to quit smoking, this has not been substantiated by other double-blind, placebo-controlled studies. There was a 74-percent reduction in the number of cigarettes smoked and a 57-percent reduction in the amount of tobacco consumed. The effective level was reported to be around 100 to 140 micrograms (μg) per 100 mL of blood. They also reported that the 25 subjects who did not want to stop smoking reduced the amount of tobacco consumed by 62 percent while there was actually an increase (by 7 percent) in the number of cigarettes smoked.

In a placebo-controlled study of 200 chronic smokers, Rapp and Olen (Ref. *4*) reported that more than 80 percent of the individuals on the drug had stopped smoking at the end of 5 to 6 days. A dose of 2 mg of the buffered lobeline sulfate was given three times a day. Less than 10 percent had stopped smoking when taking the placebo.

In addition to the Rapp studies mentioned above, the Panel was able to locate 10 other placebo-controlled studies (Refs. *5* through *14*). In only two of these (Refs. *10* and *11*) was lobeline significantly more effective than the placebo in aiding subjects to stop smoking. The other eight studies were all noncorroborative, possibly due to design defects in some of them. However, one of these (Ref. 5) employed the same study design as used in the Rapp and Olen study (Ref. *4*), but was unable to demonstrate the effectiveness of lobeline.

Since studies on lobeline sulfate as a smoking deterrent have shown conflicting results, the Panel concludes that further testing should be performed according to the testing guidelines to determine whether or not it is effective. (See part III. paragraph D. below—Data Required for Evaluation.)

(3) *Proposed dosage.* The Panel concludes that lobeline (in the form of lobeline sulfate or its pharmacological equivalent in terms of natural lobelia alkaloids or *Lobelia inflata* herb) is safe for OTC use in a dose of 2 mg up to three times a day.

(4) *Labeling.* The Panel recommends the Category I labeling for smoking deterrents. (See part III. paragraph A.2. above—Category I labeling.) In addition, because of a lack of chronic toxicity studies, the Panel recommends the following warning: "Do not use this drug for longer than 6 weeks." Any claim for longer use would require chronic toxicity studies.

(5) *Evaluation.* The Panel finds lobeline (in the form of lobeline sulfate or its pharmacological equivalent in terms of natural lobelia alkaloids or *Lobelia inflata* herb) safe for OTC use in the dosage described above, but recommends that testing of this ingredient be done according to the testing guidelines to determine whether it is effective. (See part III. paragraph D. below—Data Required for Evaluation.) These studies may be done with or without an appropriate buffer (antacids), but, if buffers are used, the protocol should be designed to show the effect of the buffer.

References

(*1*) Wright, I. S., and D. Littauer, "Lobeline Sulfate. Its Pharmacology and Use in Treatment of the Tobacco Habit," *Journal of the American Medical Association,* 109:649–654, 1937.

(*2*) OTC Volume 170038 (Section IV. c (3)).

(*3*) Rapp, G. W., B. T. Dusza, and L. Blanchet, "Absorption and Utilization of Lobeline as a Smoking Deterrent," *American Journal of Medical Sciences,* 237:287–292, 1959.

(*4*) Rapp, G. W., and A. A. Olen, "A Critical Evaluation of a Lobeline Based Smoking Deterrent," *The American Journal of Medical Sciences,* 230:9–14, 1955.

(*5*) Barlett, W. A., and R. W. Whitehead, "The Effectiveness of Meprobamate and Lobeline as Smoking Deterrents," *Journal of Laboratory and Clinical Medicine,* 50:278–281, 1957.

(*6*) Rosenberg, A., "An Attempt to Break the Smoking Habit," *Applied Therapeutics,* 4:1029–1033 and 1064, 1962.

(*7*) Scott, G. W., et al., "Buffered Lobeline as a Smoking Deterrent," *Lancet,* 1:54–55, 1962.

(*8*) Merry, J., and G. Preston, "The Effect of Buffered Lobeline Sulphate on Cigarette Smoking," *Practitoner,* 190:628–631, 1963.

(*9*) "Smoking Deterrent Study—A Report from the Research Committee of the British Tuberculosis Association," *British Medical Journal,* 2:486–487, 1963.

(*10*) Perlstein, I. B., "Smoking Deterrent Therapy in Private Practice," *in* "The First Annual M. R. Thompson Symposium on Recent Advances in the Medical Aspects of Smoking," Matthew Publishing Co., New York, pp. 40–45, 1964.

(*11*) London, S. J., "Clinical Evaluation of a New Lobeline Smoking Deterrent," *Current Therapeutic Research,* 5:167–175, 1963.

(*12*) Edwards, G., "Double-Blind Trial of Lobeline in an Anti-Smoking Clinic," *Medical Officer,* 112:158–160, 1964.

(*13*) Leone, L. A., et al., "A Study of the Effectiveness of the Smoking Deterrence Clinic," *Rhode Island Medical Journal,* 51:247–257, 260, 1968.

(*14*) Ross, C. A., "Smoking Withdrawal Research Clinics," *American Journal of Public Health,* 57:677–681, 1967.

b. *Silver acetate.* The Panel concludes that silver acetate is safe for OTC use in the dose noted below, but data are insufficient to demonstrate its effectiveness as a smoking deterrent.

(1) *Safety.* Silver acetate is one of the soluble silver salts which, with the exception of silver nitrate, have no known undesirable effects other than discoloration of the tissues, particularly the skin. Extensive animal studies in doses several times the human dose showed no evidence of any systemic effect other than staining of the tissue by the deposited silver (Ref. *1*). The Panel is unaware or any reports of toxicity in humans other than the discoloration. One reference (Ref. *2*). states:

> Silver appears to have a very low systemic toxicity. Chronic exposure to silver salts may cause argyrism (a permanent bluish discoloration of the skin or mouth) which appears to be solely of cosmetic concern. The famous "blue man" of the Barnum & Bailey Circus was said to have a total silver body burden of 90 to 100 gm. without obvious deleterious symptoms.

(2) *Effectiveness.* Silver salts are said to affect the mucous membrane of the mouth in such a way that when tobacco smoke comes in contact with these salts a nasty metallic sweet taste is produced, the effect lasting for up to 4 hours. Because of this, smoking becomes less desirable, and the individual is said to be able to reduce the number of cigarettes smoked per day.

The results of three placebo-controlled studies were submitted to support the effectiveness claim for silver acetate (Refs. *3* through *6*). The Rosenberg study was a 2-week double-blind parallel sample study involving 60 volunteers (30 in the silver acetate group and 30 in the placebo group) (Ref. *3*). This study was supplemented by Ref. *4*. In this and the other two studies cited, a chewing gum dosage form was used in order to keep the silver acetate present in the oral cavity for a relatively long period. Subjects were asked to keep a daily record of the number of cigarettes smoked each year. Weekly results were mailed or telephoned in to investigators. By the end of the 2 weeks, 11 of the 30 in the silver acetate group reported that they had stopped smoking. The difference between the stopping rates of the silver acetate and placebo group in statistically significant (p less than 0.05). The Panel believes that smoking behavior data that are reported by subjects either by telephone or by mail are not scientifically sound unless confirmed by objective measures or personal interviews. The Panel concludes that the Rosenberg study does suggest effectiveness, but does establish it.

Arvidsson (Ref. *5*) also conducted a 2-week double-blind parallel sample study. It involved 50 subjects (25 in the silver acetate group and 25 in the placebo group). Results were evaluated by comparing the mean number of cigarettes smoked on the 13th and 14th days for each group. These means were 10.6 and 18.4, for the silver acetate group and the placebo group, respectively, and the difference of 7.8 cigarettes per day is claimed to be statistically significant (p is less than 0.001). No details are given regarding the number of subjects who stopped smoking nor how the data on the number of cigarettes smoked were obtained. Again, the Panel considers this study only suggestive of effectiveness.

The third placebo-controlled study submitted was conducted by Schmidt (Ref. *6*) and consisted of 1,000 subjects who volunteered to enter a stop smoking study announced in the press and on the radio. Of the 1,000 subjects, 500 were assigned, in a double-blind fashion, to silver acetate and the other 500 to a placebo. Preparations were mailed to the subjects. Four or five weeks after this mailing, each test participant received a "validation" questionnaire. Of the 1,000 test participants, 796 returned the questionnaire. Of these, 617 questionnaires were usable (316 in the silver acetate group and 301 in the placebo group). Ninety-eight of the 316 (31.0 percent) in the silver acetate group and 75 of the 301 (24.9 percent) in the placebo group reported complete stopping of smoking. This difference is marginally significant ($p = 0.09$). No attempts to obtain information concerning stopping of smoking in the nonrespondents were attempted. While information obtained in the manner of the Schmidt study can be helpful, the Panel does not believe it can serve as a substitute for results from a well-controlled clinical study. Such a study would result from following the proposed guidelines for determining the effectiveness of OTC smoking deterrents as indicated below under "Evaluation."

(3) *Proposed dosage.* The Panel recommends a dosage of up to 6 mg silver acetate in a chewing gum every 4 hours, with not more than 6 such doses in a 24-hour period.

(4) *Labeling.* The Panel recommends the Category I labeling for OTC smoking deterrents. (See part III, paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following *"Warning"* be included in the labeling: "*Warning.* Do not use this product for longer than 3 weeks. Frequent or prolonged use of this medication may result in permanent discoloration of the skin or mouth."

(5) *Evaluation.* The Panel finds silver acetate safe for OTC use in the dosage described above, but recommends that testing of this ingredient be performed according to the testing guidelines to determine whether it is effective. (See part III. paragraph D. below—Data Required for Evaluation.)

References

(*1*) OTC Volume 170129 (Section III).

(*2*) "Clinical Toxicology of Commercial Products," 4th Ed., edited by Gosselin, R.E., et al., The Williams and Wilkins Co., Baltimore, Section II, p. 101, 1976.

(*3*) Rosenberg, L. A. "An Investigation of the Effectiveness of Tabmint, an Anti-Smoking Chewing-Gum", in section V.2., OTC Volume 170129.

(*4*) OTC Volume 170178.

(*5*) Arvidsson, T., "A Double Blind Investigation of the Effectiveness of Tabmint, an Anti-Smoking Chewing Gum," in section V.3., OTC Volume 170129.

(*6*) Schmidt, F., "Tabacco Cure by Means of Anti-Smoking Chewing Gum in a Double Blind Test," in OTC Volume 170178.

2. Category III labeling. None.

D. Data Required for Evaluation.

Guidelines for developing protocols for evaluating OTC smoking deterrents. The Panel recognizes that a generally accepted protocol for the evaluation of drugs used as smoking deterrents is not available. Further, because of the different mechanisms of action of smoking deterrents and because of the numerous other techniques (counseling and behavior modification) often used jointly with these drugs, it is impossible to develop a single protocol that would be universally appropriate. However, given the numerous methodological problems associated with attempting to evaluate these products (Refs. *1* and *2)* and considering the contradictory published results (Ref. *3*) regarding the effectiveness of these drugs and smoking withdrawal programs in general, it is imperative that well-controlled clinical trials be performed to evaluate these drugs. In designing these trials important issues must be considered carefully in order to ensure proper evaluation. To this end the Panel has developed the following guidelines to aid investigators in designing tests of effectiveness. The Panel suggests that deviations from these guidelines should be discussed with appropriate FDA personnel prior to initiating a study.

Other useful guidelines exist (Ref. *2*), but they are broader in scope than the Panel's guidelines. They deal with the evaluation of stop-smoking programs in general and not with just the evaluation of smoking deterrent drugs. Further, they deal with attempts to evaluate the effects of the various techniques in studies involving samples from the full target population (all cigarette smokers rather than long-term chronic cigarette smokers). Such studies often involve large numbers of subjects, but the Panel believes small scale, double-blind, placebo-controlled studies employing a sample population of chronic cigarette smokers who are motivated to stop smoking are sufficient to demonstrate drug effectiveness. The Panel's guidelines concern such studies.

1. *Objective of the study.* The primary objective is to determine the effectiveness of the drug under study in aiding individuals to stop smoking. The claim for some smoking deterrents is that they will aid in reducing smoking but not necessarily in stopping it. The Panel does not accept the premise that a temporary reduction in smoking has any lasting benefit and believes that it should be possible in a well-controlled study to demonstrate that a drug is

effective in aiding a significant number of individuals to stop smoking.

2. *Sample population.* The preferred sample population for the study is the population of long-term, chronic cigarette smokers who are presently heavy smokers, are motivated to stop, and have good expectations concerning the ability of drugs to be effective in aiding a person to stop smoking. "Long-term, chronic" should be taken to mean smoking regularly for at least 5 years, and "heavy smokers" should be taken to mean smoking at least 20 cigarettes per day.

If the drug is effective, it can be expected that the effectiveness should be demonstrable in the sample population described above. This population eliminates many of the problems, such as variable smoking experience, lack of motivation, and skepticism on the part of the subjects that often confound stop-smoking studies.

For any particular study the selected sample population should be fully specified and smoking habits should be thoroughly described.

3. *Study setting and investigators.* The study should be conducted by qualified investigators in clinical centers, academic settings, or private practices. The important component is the qualification of the investigator.

4. *Admissibility and exclusion criteria.* The study subjects must satisfy all the criteria of the sample population. That is, subjects must be long-term, chronic cigarette smokers who are presently heavy smokers, are well motivated, and have good expectations concerning drug effectiveness. In addition, the subjects should:

a. Be in apparent good health,

b. Have no known sensitivity to the test drug,

c. Have significantly elevated levels of carbon monoxide and thiocyanate (or nicotine and cotinine) as determined by objective measures at the beginning of the study,

d. Not have participated in similar studies within the past year,

e. Not be taking other medications, including OTC medications, which might influence the response of the subject in the study, and

f. Be able to comprehend instructions and adhere to the study protocol (take drug as required by the protocol and keep track of daily consumption of cigarettes and other tobacco products).

5. *Variables to measure in the pretest period.* Prior to giving the test medication, basic information on the subject should be obtained. This is required not only to decide upon admissibility into the study but also to use a reference point for evaluating effectiveness. The pretest variables should include:

a. Age (exact, not categorized),

b. Sex,

c. Age when started to smoke with some degree of regularity, not counting any earlier, sporadic experimentation with cigarettes,

d. Current daily rate of cigarette smoking when entering treatment and use of other tobacco products, if any (exact number of cigarettes should be requested),

e. Appropriate objective measurements (carbon monoxide and blood thiocyanate levels) should be taken at two different pretest times,

f. Education,

g. Previous attempts to stop smoking (number of attempts, time since last attempt, degree of success at last attempt, number of times systematic help sought (a smoking clinic)),

h. Motivation (desire and commitment to stop),

i. Level of expectation concerning the ability of drugs to be effective in aiding a person to stop smoking,

j. Attitudes towards smoking, and

k. Knowledge of detrimental effects of smoking.

6. *Study design.* The study design must be randomized, double-blinded, and placebo-controlled. A parallel sample design appears to be preferred over a crossover design. Since a successful treatment with an effective drug results in stopping smoking, the subject does not necessarily return to smoking after the treatment period. Crossover designs are employed usually in situations where there is a return of the subject to smoking.

7. *Length of the study.* The length of the study should be at least 4 weeks: 1 week of pretest and at least a 3-week study period. It is not necessary that the drug be taken for 3 weeks. However, an evaluation of effectiveness should take place at least 3 weeks after the drug was started. Any difference between the drug and placebo for periods shorter than this may be statistically significant, but cannot be considered clinically significant.

8. *Variables to measure during the study.* A daily diary should be kept in which is recorded:

a. The amount and times of taking the test drug,

b. The number of cigarettes smoked each day,

c. Any significant change in lifestyle or environment which results in an increased or decreased exposure to carbon monoxide, and

d. The use of any other tobacco product.

9. *Effective measures.* The only effectiveness variable is to stop smoking. In computing the proportion of those who stop smoking the denominator should be all those who were originally in the study group (placebo or drug) and not just those completing the study. Absolute levels of and changes in baseline objective measurements are essential. Data should be obtained from the subjects in a face-to-face interview and should not be obtained via mailings or telephone conversations.

10. *Statistical tests and sample sizes.* Appropriate statistical tests should be used to establish effectiveness. The analysis comparing the drug and placebo groups should include at least the "two independent sample difference in proportions test" where the dependent variable is the dichotomous variable, "cessation of smoking or not" (Ref. *4*). In addition, analyses of the objective data (carbon monoxide and thiocyanate levels) are imperative. Also, analyses investigating the relation of stopping smoking to age, sex, education, etc. should be performed. Statistical analyses techniques such as logistic regression are appropriate here.

Sample sizes for the drug and placebo groups should be determined to give a p value of 0.05 for testing equality of effectiveness of the drug and placebo and a sufficiently small probability of error of not detecting a significant clinical superiority of the drug over the placebo (a Type II error of 0.2). The drug company should be prepared to discuss what it means by a significant clinical superiority, of the drug over the placebo (a Type II error of 0.2). The drug company should be prepared to discuss what it means by a significant clinical superiority.

11. *Followup.* Effectiveness should be established at the end of 3 weeks. If a claim for long-term effectiveness is made, the smoking status of the subjects should be evaluated at the end of 4 months. Recidivism is greatest within 4 months (Ref. *2*), and this followup will indicate long-term effectiveness of the treatment. The Panel recommends but does not require that there be a 4-month followup of all subjects.

12. *Drop-outs.* The entire study population must be accounted for at all points of data collecting, including the followup. Persons who cannot be reached for evaluation should be counted as failures (smokers), rather than assuming that those who respond are representative of the total study group.

13. *Number of clinical trials.* Two separate trials should be conducted by

different investigators at different geographical sites. The samples from each of these sites should be representative of the sample population.

References

(1) "Smoking and Health. A Report of the Surgeon General," U.S. Department of Health, Education, and Welfare, DHEW Publication No. (PHS) 79–50066, 1979.

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

(3) Schwartz, J. L., "A Critical Review and Evaluation of Smoking Control Methods," *Public Health Reports*, 84:483–506, 1969.

(4) Dixon, W. J., and F. J. Massey, Introduction to Statistical Analysis, 3d Ed., McGraw-Hill, New York, p. 249, 1969.

Therefore, under the Federal Food, Drug, and Cosmetic Act (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)), and the Administrative Procedure Act (secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554,702, 703, 704)), and under 21 CFR 5.11 (see 46 FR 26052; May 11, 1981)), the agency advises in this advance notice of proposed rulemaking that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations would be amended by adding in Part 357, a new Subpart G, to read as follows:

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

Subpart 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); secs. 4, 5, and 10, 60 Stat. 238 and 243 as amended (5 U.S.C. 553, 554, 702, 703, 704).

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 of this chapter.

(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 which helps one to stop smoking cigarettes.

§ 357.610 Smoking deterrent active ingredients. [Reserved]

§ 357.650 Labeling of smoking deterrent drug 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 contains a statement of the indications under the heading "Indications" that is limited to one or more of the following statements:

(1) "A temporary aid to those who want to stop smoking cigarettes."

(2) "Helps you stop the cigarette urge temporarily."

(3) "Helps you stop smoking cigarettes temporarily."

(4) "A temporary aid to breaking the cigarette habit."

(5) *Other required statement.* The labeling of the product contains the following statement: "This product's effectiveness is directly related to the user's motivation to stop smoking cigarettes."

(6) *Other allowable statement.* The labeling of the product may contain a description (in lay language) of the specific proven mechanism of action of the active ingredients under the heading "Mechanism of Action."

(c) *Warnings.* [Reserved]

(d) *Directions.* [Reserved]

Interested persons may, on or before April 5, 1982, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments on this advance notice of proposed rulemaking. Three copies of any comments are to be submitted, except that individuals may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document. Comments replying to comments may also be submitted on or before May 5, 1982. Received comments may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

Dated: September 23, 1981.

Arthur Hull Hayes, Jr.,

Commissioner of Food and Drugs.

Dated: December 17, 1981.

Richard S. Schweiker,

Secretary of Health and Human Services.

[FR Doc. 82–2 Filed 1–4–82; 8:45 am]

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