DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 357

[Docket No. 81N-0064]

Deodorant Drug Products for Internal Use 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) deodorant drug products for internal use 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 June 7, 1980 a report on OTC deodorant drug products for internal use from the Advisory Review Panel on OTC Miscellaneous Internal 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 deodorant drugs products for internal use 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.

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 judgement 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 deodorant drug products for internal use 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 deodorant drug products for internal use 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 deodorant drug products for internal use. 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 necessary, if any. Comments regarding the impact of this rulemaking on OTC deodorant drug products for internal use 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 deodorant drug products for internal use 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 misbanded (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. The list, which did not include ingredients in deodorants for internal use, 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 drug 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 data and 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 followed 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 Ralph B. D'Agostino, Ph. D., for advice in 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 deodorant drug products for internal use in this document. The review of 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 deodorant drug products for internal use were discussed were held on: March 2 and 3, April 17 and 18, June 2, and 3, July 21, September 29 and 30, December 8 and 9, 1979; February 23 and 24, April 18 and 19, and June 6 and 7, 1980.

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

The following persons were requested by the Panel to appear to express their views on deodorant drug products for internal use:

Donald P. Binder
Norma N. Gill, E.T.
Rupert B. Turnbull, M.D.

No person who so requested was denied an opportunity to appear before the Panel to discuss deodorant drug products for internal use.

The Panel has thoroughly reviewed the literature and data submissions, has listened to additional testimony from interested persons, and has considered all pertinent data and information submitted through June 7, 1980 in arriving at its conclusions and recommendations for OTC deodorant drug products for internal use.

In accordance with the OTC drug review regulations (21 CFR 330.10), the Panel considered OTC deodorant drug products for internal use with respect to the following three categories:

Category I. Conditions under which OTC deodorant drug products for internal use are generally recognized as safe and effective and are not misbranded.

Category II. Conditions under which OTC deodorant drug products for internal use are not generally recognized as safe and effective or are misbranded.

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

The Panel reviewed three active ingredients in OTC deodorant drug

products for internal use and classified all three 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) requested the submission of data on OTC miscellaneous internal drug products, the following firms made submissions related to deodorant drug products for internal use:

A. Submissions by Firms

Firms and Marketed products

Requa Manufacturing Co., Inc., Greenwich, CT 06830—Requa's Activated Charcoal capsules and tablets.

Rystan Co., Inc., White Plains, NY 10605—Derefil tablets and Chloresium tablets.

The Parthenon Co., Inc., Salt Lake City, UT 84119—Devrom chewable tablets.

B. Labeled Ingredients Contained in Marketed Products Submitted to the Panel

Bismuth subgallate
Charcoal, activated
Chlorophyllin, water-soluble

C. Classification of Ingredients

1. *Active ingredients.*
Bismuth subgallate
Charcoal, activated
Chlorophyllin, water-soluble

2. *Inactive ingredients.*
None.

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, Rm. 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. *Colostomy.* An external operative opening from the colon.

2. *Deodorant for internal use.* An ingredient taken internally to render offensive odors less perceptible.

3. *Enterostomates.* Those persons who have an opening into the intestine through the abdominal wall, e.g., a colostomy or ileostomy.

4. *Ileostomy.* An external operative opening from the ileum.

5. *Incontinent patients.* Those persons who are unable to control the elimination of urine or feces.

6. *Ostomate.* General terminology referring to a person who has an operative ostomy.

7. *Ostomy.* General term referring to any operative opening for the external discharge of urine or feces.

B. General Discussion

Since antiquity, humans have been bothered by the problem of body odors, most of which can be controlled or diminished by adequate personal hygiene. But there are conditions over which individuals do not have complete control, such as when an individual has an ostomy or when individuals are incontinent. In such cases, it has been advocated by some that drugs be administered internally to control the offensive odor produced. Others believe that odors related to urinary and fecal incontinence can be controlled by attention to dietary intake and adequate fluid intake as well as adequate personal and environmental hygiene. Still others believe that ostomy odors can be controlled by the use of external appliances with or without deodorants. Odors of emissions from enterostomies are primarily due to bacterial action on food residues. Such bacterial action takes place in the colon. Hence, odors from enterostomy emission are mainly confined to colostomies.

The Panel reviewed three ingredients, bismuth subgallate, activated charcoal, and water-soluble chlorophyllin, intended as deodorants for internal use and reviewed specific claims for reducing or controlling enterostomy odor, urinary or fecal incontinence odor, body odor, and the odor of surface lesions. Very little data were available for review on the two latter claims; therefore, the Panel has concentrated its review on claims for reduction of enterostomy odor and urinary or fecal incontinence odor.

The Panel believes that a deodorant for internal use should be capable of significantly decreasing odors which are not related to faulty personal hygiene. The Panel has followed this principle in reviewing the specific ingredients for effectiveness and in establishing the testing guidelines for these ingredients.

C. Labeling

The Panel has carefully reviewed the submitted labeling claims for products promoted as deodorants for internal use and has categorized them in Category I, Category II, or Category III. The Panel realizes that other terms may be developed to express the same Category I indications. Only those indications 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) 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 drug products, and recommends that the industry make the necessary effort to design labeling which is legible.

One of the functions of this Panel is to attempt to eliminate improper labeling claims. Some of the labeling on drug products currently marketed as deodorants for internal use is unsupported by scientific data, and, in some cases, is misleading. 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.

The Panel believes that if two ingredients are indistinguishable with regard to effectiveness, it is misleading to claim superiority for one of the ingredients. Undocumented or misleading claims such as "Prompt reduction * * *" and colloquial or provincial expressions that do not have meaning to most people must not be used. In the labeling, effectiveness should not be related to the taste, odor, consistency, or other physical characteristics of the product, except as these physical characteristics may relate to the action of the active ingredients.

The Panel is aware of the current OTC labeling regulation dealing with warning statements in § 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 labeling of drug products indicated as deodorants for internal use. However, the Panel recommends that the other warning statement required by § 330.1(g), "In case of accidental overdose, seek professional assistance or contact a Poison Control Center immediately," be revised to read as follows: "In case of accidental overdose, contact a Poison Control Center, emergency medical

facility, or doctor immediately for advice." The Panel believes that this revision will be more informative to the consumer.

Since OTC drug products can be purchased by anyone, it is the view of the Panel that the public may not regard them as products which can result in injurious or potentially serious consequences if used improperly. 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 toxicity that warrant discontinuing use of the drug.

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 and that it should clearly indicate 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 per dose.

III. Deodorant Drug Products for Internal Use

A. Category I Conditions

The following are Category I conditions under which OTC deodorant drug products for internal use 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 as Category I, it recommends the following Category I labeling for deodorant drug products for internal use in the event that one or more ingredients are found to be generally recognized as safe and effective and not misbranded.

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

(1) "A colostomy or ileostomy deodorant."
(2) "An aid to reduce odor from colostomies or ileostomies."

b. *Other required statement.* All product labeling shall contain the following statement: "This product cannot be expected to be effective in the reduction of odor due to faulty personal hygiene."

B. Category II Conditions

The following are Category II conditions under which a deodorant drug product for internal use is not generally recognized as safe and effective or is misbranded.

1. *Category II active ingredients.* None.

2. *Category II labeling.* The Panel concludes that some labeling claims for deodorants for internal use are either vague, misleading, or unsupported by scientific data. The claims listed below and other related terms are therefore classified as Category II labeling for deodorant drug products for internal use.

a. "For the control of breath and body odors."
b. "To reduce breath and body odors."
c. "For the control of odor from surface lesions."
d. "To reduce odor from surface lesions."
e. "For management of mouth, breath, and body odors."
f. "For prompt reduction of oral malodors caused by foods, beverages, tobacco, catarrh, and other sources."
g. "For the control of perspiration odors (underarm, feet, and crotch) and bad breath."
h. "An internal deodorant."

The claim "To reduce body (perspiration) odor or surface lesion odor" has been placed in Category III labeling but only for water-soluble chlorophyllin. (See part III. paragraph C.2. below—Category III labeling.)

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.*

Bismuth subgallate.
Charcoal, activated.
Chlorophyllin, water-soluble.

a. *Bismuth subgallate.* The Panel has reviewed the use of bismuth subgallate as a deodorant for internal use for reducing enterostomy odors and concludes that it is safe for OTC use in the dosage proposed below, but data are insufficient to demonstrate its effectiveness.

(1) *Safety.* The bismuth salts, which have been used internally to reduce the odor of feces and gases released from the intestinal tract, are relatively insoluble. The majority of people who use such a product have an ileostomy or colostomy resulting from surgery for a pre-existing illness.

Injectable bismuth salts have been used in the past for treatment of syphilis and other conditions, and nephrotoxicity related to bismuth overdose has been well documented. In 1974, a different type of toxic reaction was reported in Australia in which the chronic ingestion of bismuth subgallate resulted in a severe, chronic, reversible encephalopathy (Ref. *1*). Bismuth subnitrate was indicated in France in six reported cases of reversible encephalopathy (Ref. *2*). By 1976, Martin-Bouyer (Ref. *3*) had recorded in France 360 cases of intoxication associated with chronic ingestion of various bismuth salts (subnitrate, silicate, aluminate, carbonate, basic nitrate, subgallate, subcarbonate, aluminol silicate, phosphate, oxyquinolate, pectate, and citrate). These cases involved 294 persons, of whom 16 died. Four cases of encephalopathy associated with bismuth subgallate were reported by Burns, Thomas, and Barron (Ref. *4*). The Panel is not aware of any reports of such incidents occurring in the United States. Although these salts of bismuth are considered relatively insoluble and poorly absorbed from the gastrointestinal tract, there is a significant absorption of some bismuth salts by some people (Refs. *2* and *5*). Factors controlling this absorption have not been explained; however, a decline of blood levels of bismuth correlates well with the degree of clinical improvement of the encephalopathy syndrome (Ref. *5*). Symptoms and signs commonly associated with the syndrome are asthenia (generalized weakness and fatigue), tremor, unsteadiness, muscular discomfort, loss of memory, confusion, and intellectual impairment. These disappear weeks to months after bismuth salt ingestion is discontinued.

Although these reactions have occurred in France and Australia following chronic ingestion of very high doses of bismuth preparations, this Panel is not aware of any such occurrences in the United States with bismuth subgallate when used at a maximum dose of 1.6 grams (g) per day (200 to 400 milligrams (mg) four times daily). This was verified by presentations to the Panel at its July 21, 1979 meeting (Ref. *6*). It should also be noted that at the time Australia was experiencing cases of bismuth-induced encephalopathy it was importing all its bismuth from France. Since 1977, when the importation of French bismuth was prohibited, Australia has not experienced a single case of bismuth-induced encephalopathy (Ref. *7*).

The Panel is aware that bismuth preparations other than bismuth subgallate have been used for neutralizing enterostomy odors; but, because they have been used to a considerably lesser degree than bismuth subgallate and because the Panel found very little information on which to base any conclusions, they will not be evaluated here.

(2) *Effectiveness.* The use of bismuth subgallate as an enterostomy deodorant

has been recommended by several well-recognized experts on ostomy care. However, there are few clinical studies to support this view. In one double-blind study bismuth subgallate was reported to be statistically significantly better than placebo (p less than 0.01) when used by ileostomates in a dosage of 400 mg before meals to control odor (Refs. *8* and *9*). The details of the study were not available.

In another study, which was uncontrolled, questionnaires were sent to 100 ostomy patients, both ileostomates and colostomates, concerning their use of bismuth subgallate (Ref. *10*). Forty-nine responses (41 from ileostomates and 8 from colostomates) were received, of which 23 (21 ileostomates and only 2 colostomates) indicated a significant use of bismuth subgallate. Of these, 13 (12 ileostomates and 1 colostomate) found the product to be very effective or completely effective in reducing enterostomy odor.

These studies, in addition to presentations made to the Panel on July 21, 1979, give some indication that bismuth subgallate may be effective as an enterostomy deodorizer (Ref. *6*). However, conclusive proof has not been established. This is based on the well-known fact that ileostomy odors are minor as compared to colostomy odors. The Panel recommends that further testing be done according to the proposed testing guidelines to determine whether or not bismuth subgallate is effective as an enterostomy deodorant.

(3) *Proposed dosage.* The Panel concludes that bismuth subgallate is safe for OTC use in a dose of 200 to 400 mg up to four times daily.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used as deodorants for internal use. (See part III. paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel concludes that bismuth subgallate as generally recognized as safe for OTC use in the proposed dosage noted above, but finds insufficient data to demonstrate its effectiveness as a deodorant for internal use for reducing enterostomy odors. The Panel, therefore, recommends that it be tested according to the proposed testing guidelines. (See part III. paragraph D. below—Data Required for Evaluation.)

References

(*1*) Morgan, F. P., and J. J. Billings, "Is This Subgallate Poisoning?," *Medical Journal of Australia*, 2:662–663, 1974.

(*2*) Buge, A., et al., "Encephalopathies myocloniques par les sels de bismuth," *La Nouvelle Presse Medicale*, 3:2315–2320, 1974.

(*3*) Martin-Bouyer, G., "Intoxications par les sels de Bismuth administres par voie orale. Enquete epidemiologique," *Therapie*, 31:683–702, 1976.

(*4*) Burns, R., D. W. Thomas, and V. J. Barron, "Reversible Encephalopathy Possibly Associated with Bismuth Subgallate Ingestion," *British Medical Journal*, 1:220–223, 1974.

(*5*) Boiteau, H. L., et al., "Relations entre l'evolution des encephalopathies bismuthiques et les taux de bismuth dans le sang et dans les urines," *European Journal of Toxicology*, 9:233–239, 1976.

(*6*) Summary Minutes of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products meeting held on July 21, 1979.

(*7*) Buge, A., et. al., "Correlations Evolutives: Cliniques Electroencephalographiques, tomodensitometriques et toxicologiques, Dans Cinq Cas D'Encephalopathies bismuthiques," *La Semaine Des Hopitaux De Paris*, 55:1466–1472, 1979.

(*8*) Sparberg, M., "Bismuth Subgallate as an Effective Means for the Control of Ileostomy Odor: A double-Blind Study," *Gastroenterology*, 66:476, 1974.

(*9*) Sparberg, M., additional information regarding his study titled "Bismuth Subgallate as an Effective Means for the Control of Ileostomy Odor: A Double-Blind Study" contained under cover letter dated September 18, 1979 in Panel Administrator's File (OTC Volume 17HPAII).

(*10*) OTC Volume 170172 (uncontrolled study conducted by M. Goldsmith and N. Gill).

b. *Charcoal, activated.* The Panel has reviewed activated charcoal as a deodorant for internal use for reducing enterostomy gas and odor and concludes that it is safe for OTC use in the dosage proposed below, but data are insufficient to demonstrate its effectiveness for this use.

(1) *Safety.* There is no information available to the Panel indicating that activated charcoal is harmful for human use. Chronic ingestion by uremic patients in doses up to 50 g daily for up to 20 months produced no apparent ill effects (Ref. *1*). Vitamin deficiency has been induced in chicks on a diet containing 2 percent charcoal (Ref. *2*) and in rats (Refs. *3*, *4*, and *5*), presumably as a result of adsorption of nutrients by the charcoal. Because of the large amounts of charcoal used in these studies, plus the absence of reports of similar vitamin deficiencies in humans who have taken activated charcoal for relatively long periods of time, the Panel believes that the probability of nutrient deficiency in humans when taking activated charcoal is remote. However, the Panel is concerned that activated charcoal, due to its nonspecific adsorptive capacity, will adsorb ingested drugs, thereby decreasing their pharmacological activity. Therefore, the Panel recommends that the labeling of activated charcoal, when intended as an enterostomy deodorant, include a drug interaction precaution regarding any concurrent drug therapy.

The Panel has also reviewed activated charcoal as a digestive aid and for the treatment of acute toxic ingestion.

(2) *Effectiveness.* Activated charcoal has a long history of use as an effective adsorbent in various medical, industrial, and home situations. This Panel has previously reviewed the use of activated charcoal in the treatment of acute toxic ingestion and found it to be effective. The Panel has received one submission regarding the use of activated charcoal as a deodorant for internal use to reduce enterostomy gas and odor (Ref. *6*). As supporting evidence of this claim, the same firm referred to a study (Ref. *7*) submitted to the Panel when it previously reviewed digestive aid drug products. This was a preliminary double-blind study which indicated that activated charcoal would reduce the incidence of gas in normal healthy males after a meal containing beans, but no mention is made of the odor or the volume of the gas released.

Despite the absence of convincing double-blind studies or other scientific proof of effectiveness of activated charcoal as an enterostomy deodorant, the Panel believes it is reasonable to assume that the claims of its effectiveness for reducing gas and thereby reducing enterostomy odor are in keeping with its scientifically proven adsorptive capability (Ref. *8*). This opinion was also expressed in the presentations made to the Panel on July 21, 1979 (Ref. *9*).

On the basis of evidence presented as to the high adsorptive capability of activated charcoal also and the expert knowledge of the Panel, the Panel concludes that activated charcoal may be effective as a deodorant for internal use for reducing enterostomy gas and odor. The Panel recommends that further testing be done according to the proposed testing guidelines to determine whether or not activated charcoal is effective for such use.

(3) *Proposed dosage.* The Panel concludes that activated charcoal is safe for OTC use in a dose of up to 10 g daily in divided doses.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used as deodorants for internal use. (See part III. paragraph A.2. above—Category I labeling.) In addition, the Panel recommends that the following statement be included in a "Drug Interaction Precautions" section: "Because this medication may decrease the effectiveness of any other drug you are taking, consult your doctor before using it."

(5) *Evaluation.* The Panel concludes that activated charcoal is generally recognized as safe for OTC use in the dose noted above, but finds insufficient data to demonstrate its effectiveness as a deodorant for internal use for reducing enterostomy odor and gas. The Panel recommends that this ingredient be tested according to the proposed testing guidelines. (See part III. paragraph D. below—Data Required for Evaluation.)

References

(1) Yatzididis, H., "Activated Charcoal Rediscovered," *British Medical Journal,* 4:51, 1972.

(2) Almquist, H. J., and D. Zander, "Adsorbing Charcoal in Chick Diets," *Proceeding of the Society of Experimental Biology and Medicine,* 45:303–305, 1940.

(3) Cailleau, R., and J. Adrian, "L'Influence du Charbon sur L'Efficacite Vitaminique d'un Regime Equilibre," *Bulletin de la Societe Scientifique d'Hygiene Alimentaire et d'Alimentation Rationelle,* 36:114–121, 1948.

(4) Messerli, N., "De L'Influence des Substances Adsorbantes Ajoutees A une Alimentation Unilaterale sur le Developpement de L'Etat D'Avitaminose," *Archives Internationales de Physiologie (Liege),* 19:103–114, 1922.

(5) Matet, A., and J Matet, "Regimes au Charbon Actif et Avitaminose A Precoce. Application a la Preparation de Regimes sans Vitamine A," *Bulletin de la Societe de Chemie Biologique,* 27:513–518, 1945.

(6) OTC Volume 170179.

(7) Hall, R. G., "Effectiveness of Charcoal in the Treatment of Intestinal Flatus," in Part III, OTC Volume 170151.

(8) OTC Volume 170125.

(9) Summary Minutes of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products meeting held on July 21, 1979.

c. *Chlorophyllin, water-soluble.* The Panel has reviewed water-soluble chlorophyllin, which according to New and Nonofficial Remedies (Ref. *1*) is 100 percent potassium sodium copper chlorophyllin, as a deodorant for internal use and concludes that it is safe for OTC use in the dosage proposed below, but data are insufficient to demonstrate its effectiveness in reducing enterostomy odor, urinary or fecal incontinence odor, body odor, or the odor from surface lesions.

(1) *Safety.* The median lethal dose (LD_{50}) for oral ingestion of a 15-percent aqueous solution of potassium sodium copper chlorophyllin for mice was found to be 7 grams per kilogram (g/kg) body weight. No toxic effects were found in rats from long-term feeding of a diet containing a 3–percent concentration of this chlorophyllin. There were no adverse effects on growth, survival, ability to conceive, or survival of offspring (Ref. *2*).

Few side effects have been reported in humans following the administration of water-soluble chlorophyllin in oral doses of up to 800 mg (in divided doses) daily for varying durations, each exceeding 1 week (Refs. *3* through *7*). The most frequent side effect reported was mild diarrhea, along with an expected green coloration of the stools. There was also one case of abdominal cramps and one case of excessive gas.

Acceptable daily intake of up to 15 mg/kg of a cholorophyllin copper complex, sodium and potassium salts, was established as temporarily acceptable by the Expert Committee on Food Additives of the World Health Organization (Ref. *8*).

(2) *Effectiveness.* The Panel was unable to find any well-controlled clinical studies demonstrating a reduction of enterostomy odor, urinary or fecal incontinence odor, body (perspiration) odor, or odor from surface lesions by the oral ingestion of water-soluble chlorophyllin.

The Panel is aware of 4 reports of uncontrolled clinical trials with a total of 47 enterostomy patients in which it was claimed that 46 had marked decrease or absence of odor from the ostomies with varying doses of water-soluble chlorophyllin (Refs. *6, 7, 9,* and *10*).

The Panel is also aware of 6 reports of uncontrolled clinical trials on the use of water-soluble chlorophyllin as a deodorant for internal use in a total of some 300 fecal or urinary incontinent patients in psychiatric institutions or nursing homes. The doses ranged from 100 to 200 mg daily. The odor was reported to be markedly reduced or absent within 1 to 2 weeks (Refs. *3, 4, 5, 10, 11,* and *12*).

Two of the studies mentioned above also showed good results in the reduction of body odor (Ref. *5*) and odor from malodorous surface lesions (Refs. *5* and *6*).

The studies summarized above, involving several hundred patients, reported excellent efficacy of water-soluble chorophyllin in multiple doses for the control of odors. From a statistical point of view, all of these studies were defective and the conclusions are unacceptable. Some of the defects which are common to the nine studies are as follows:

(a) None of the studies was double-blinded. (The investigators always knew whether the subjects were receiving the drug.)

(b) None of the studies properly employed placebos. Golden and Burke (Ref. *5*) apparently employed a placebo intermittently; however, this was not done in any systematic way. A crossover study employing a placebo could be performed easily to evaluate these drugs, but this was not done.

(c) It cannot be ascertained if proper controls were applied to minimize the effects of confounding variables, such as patient hygiene and patient care. It is unknown if the successes reported were due to the drug or to these variables.

(d) Only one study appears to have attempted to evaluate in quantitive terms the outcome/success variables dealing with reduction of odors (Ref. *12*).

Most of the studies reported simply state that odors were reduced or eliminated. No attempts were made to quantify baseline odors and changes over time. Thus, the results of the studies cannot be evaluated by statistical procedures. Further, their validity and reliability cannot be established in any objective manner.

Much of the odor of feces is due to the production of malodorous hydrogen sulfide. An in vitro test with water-soluble chlorophyllin has demonstrated a decrease of fecal odor (possible by adsorption of hydrogen sulfide) and the inhibition of the production of hydrogen sulfide in cultures of hydrogen sulfide-producing enteric organisms (Ref. *13*). The author attributes the mechanism of deodorization to a change in the bacterial metabolism.

A double-blind investigation on the systemic control of chronic foul foot odor in 88 psychiatric patients over a 4-week period shows no significant differences in subjective evaluation of the intensity of odor following administration of chlorophyll or placebo (Ref. *14*). There is no indication as to exactly what chlorophyll preparation was used in this study, nor is there any mention of the strength used.

The Panel concludes that there is insufficient evidence to demonstrate the effectiveness of water-soluble chlorophyllin as a deodorant for internal use for reducing enterostomy odor, urinary or fecal incontinence odor, body odor, or the odor from surface lesions, and recommends that it be tested further according to the proposed testing guidelines to determine whether or not it is effective.

(3) *Proposed dosage.* The Panel concludes that the water-soluble chlorophyllin is safe for OTC use up to 800 mg daily in divided doses.

(4) *Labeling.* The Panel recommends Category I labeling for ingredients used as deordorants for internal use. (See part III. paragraph A.2. above—Category I labeling.)

(5) *Evaluation.* The Panel concludes that water-soluble chlorophyllin copper chlorophyllin) is safe for OTC use in the proposed dosage stated above, but finds insufficient data to demonstrate its effectiveness as a deodorant for internal

use for reducing enterostomy odor, urinary or fecal incontinence odor, body odor, or the odor from suface lesions. The Panel, therefore, recommends that it be tested according to the proposed testing guidelines. (See part III. paragraph D. below—Data Required for Evaluation.)

References

(1) "New and Nonofficial Remedies," J.B. Lippincott Co., Philadelphia, p. 570, 1957.

(2) Harrison, J. W. E., S. E. Levin, and B. Trabin, "The Safety and Fate of Potassium Sodium Copper Chlorophyllin and Other Copper Compounds," *Journal of American Pharmaceutical Association*, 43:722–737, 1954.

(3) Morrison, J. E., "Oral Tablets Help Control Ward Odors, Study Shows," *Hospital*, 33:97, 1959.

(4) Laitner, W., "Odor Control in the Incontinent Mental Patient," *Phychiatric Quarterly*, (Supplement 2), 29:190–192, 1055.

(5) O'Connell, I., "A Useful Adjunct for Odor Control in Malodorous Surface Lesions and Incontinence," *Journal of the Central Islip State Hospital*, 1:23–26, 1968.

(6) Golden, T., And J. F. Burke, "Effective Management of Offensive Odors" *Gastroenterology*, 31:260–265, 1956.

(7) Siegel, L. H., "The Control of Ileostomy and Colostomy Odors," *Gastroenterology*, 38:634–636, 1960.

(8) The Eighteenth Report of the Joint FAO/WHO Expert Committee on Food Additives, *World Health Organization Technical Report Series*, No. 557, pp. 16–17, 1974.

(9) Weingarten, M., and B. Payson, "Deodorization of Colostomies with Chlorophyll," *The Review of Gastroenterology*, 18:602–604, 1951.

(10) Joseph, M., "The Control of Fecal Odors with Chlorophyll Tablets," *Western Journal of Surgery, Obstetrics and Gynecology*, 60:363–364, 1952.

(11) Dory, A. E., "The Control of Odor in Urinary Incontinence," *Nursing Homes*, 20:28, 1971.

(12) Noonan, L., "Summary of Derifil Tablets Trial," Rockland State Hospital, Orangeburg, NY, April 1972 (unpublished) contained in OTC Volume 170014 (Exhibit Y).

(13) Coren, O. J., and R. D. Barnard, "Probable Mechanism of Bowel Content Deodorization by Chloresium Ingestion. A confirmatory Bacteriologic Study," *New York State Journal of Medicine*, 54:2195–2199, 1954.

(14) Blake, R., "Determination of Extent of Deodorizing Properties of Chlorophyll," *Journal of American Podiatry Association*, 58:109–112, 1968.

2. *Category III labeling.* The Panel concludes that data are insufficient to demonstrate the effectiveness of internal deodorants in reducing the odor associated with incontinence or to reduce gas in enterostomy conditions. for water-soluble chlorophyllin, data are also insufficient to demonstrate effectiveness for reducing body (perspiration) odor or surface leasion odor. The following labeling claims are placed in Category III:

a. "For the reduction of fecal or urinary odor associated with incontinence."

b. "To reduce gas and odor associated with enterostomies."

c. *For products containing water-soluble chlorophyllin.* "To reduce body (perspiration) odor or surface lesion odor." Similar claims for other deodorants for internal use have been classified as Category II. (See part III. paragraph B.2. above—Category II labeling.)

D. Data Required for Evaluation

Guidelines for developing protocols for evaluating OTC deodorant drug products for internal use. The Panel recognizes that currently there is not available a generally accepted protocol for evaluating OTC deodorants for internal use. The Panel has reviewed carefully the scientific literature and has not been able to find any well-controlled studies for these drugs. Still, in order to bring a Category III drug into Category I, well-controlled studies must be performed. To aid investigators in designing tests of effectiveness, the Panel has developed the following guidelines. These guidelines are restricted to studies whose target population is subjects with enterostomies, and they are not meant necessarily to extend to other populations (e.g., to incontinent patients); however, many of the principles established here would be applicable. The guidelines are not meant to be definitive even for the target population of enterostomates. There may be at present or in the future other appropriate techniques, advances, or improved methodologies not contained here. However, these quidelines illustrate the important issues that must be considered in clinical trials involving the present set of drugs and, for that reason, should be a useful aid to investigators. The Panel would have preferred to use an objective measure to detect odor produced but is not aware of the availability of any practical methodology of adequate sensitivity and, therefore, is relying on the sense of smell, which is obviously subjective.

The Panel suggests that investigators discuss with appropriate FDA personnel proposed deviations from the following guidelines, as well as studies directed at other target populations, prior to initiation of such studies.

1. *Objective of the study.* The objective of the study is to determine whether the drug under investigation is more effective than a placebo as a deodorant for internal use for reducing colostomy odor.

2. *Target and sample populations.* The target population is the population of enterostomates who perceive a need for an internal deodorant to control odors that are not due to faulty personal hygiene. For the study, the sample population should consist only of individuals with colostomies. Odor is more likely to be a problem with these individuals than with other ostomates (e.g., ileostomates). Restriction of a study to this sample population will eliminate the potential of having many individuals in the study who do not have an odor problem and for whom a clinically significant drug effect will be impossible to document. If the drug is effective, it can be expected that its effectiveness will be demonstrable in a sample of colostomates. Further, if the drug is effective for these individuals, the Panel believes it should also be effective for the full target population of enterostomates.

For any particular study, the selected sample population should be fully specified, and pertinent characteristics should be thoroughly described. Also, the appropriate target population to whom study results can be extended should be stated, and the logic underlying the extension should be justified.

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 should be individuals with colostomies (other ostomates are to be excluded). In addition, the subjects

a. Should be free of active disease,

b. Should have no known sensitivity to the test drug,

c. Should not be taking other medications, including OTC medications, which might influence the response of the subject in the study,

d. Should be able to comprehend instructions and adhere to the study protocol (e.g., take drug as required by the protocol and keep a daily diary), and

e. Should not have an odor problem that might be related to faulty personal hygiene.

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

a. Subjective measure of odor, on a 0 to 4 scale with 0 representing no odor and 4 representing maximum odor, by at least two individuals (subject and, for example, a staff member),

b. Enumeration of physical hygiene measures (e.g., type of colostomy appliance used),

c. Frequency of change of colostomy appliance,

d. Frequency of use of external deodorants in colostomy appliance, and

e. Quantification of dietary and other factors that may impact on odor.

Other variables, such as age, sex, and health status of the subjects, that are routinely of interest in clinical studies should also be collected at the prestudy stage.

6. *Study design.* The study should be randomized, double-blind, placebo-controlled crossover. Subjects should first go for 1 week without any treatment and then be randomly assigned to one treatment for a period of 14 days (½ to the drug and ½ to the placebo). This should be followed by a 7-day washout period and then subjects should be crossed over to the other treatment for a second period of 14 days.

7. *Instruction to study subjects.* The subjects should be given instructions for drug use according to the drug company's directions. The investigator should be certain the instructions are understood. Further, in order to insure consistency throughout the study, very strict rules to exclude variations in personal hygiene should be included in the instructions to the subjects. The use of external deodorants should be eliminated. Also, in order to produce the proper setting to judge the drug's effectiveness, the investigator may want to include the use of odor-producing foods in the diet during the course of the study. If this is desirable, the type and amount of food should be standardized by subject and should be uniform in both stages of the crossover.

8. *Variables to measure during the study.* A daily diary should be kept to record the amounts and times of day that the treatment (drug or placebo) is taken. Daily food intake and changes in hygiene should also be recorded. Also, a subjective measure of odor should be recorded daily by the individual. As in the prestudy measure, this should be on a 0 to 4 scale with 0 representing no odor and 4 representing maximum odor. Further, the subjects should be interviewed by a member of the project staff once at the beginning, once during, and once at the end of each of the 14-day periods (six interviews). During these interviews a rating on the 0 to 4 scale of the subject's odor should be made by a project staff member.

9. *Effectiveness measures.* The Panel recognizes that a subject's ability to measure his personal odor will lessen with time, but believes that the primary measure of odor in the study should be subject's own perception of it. This should be supplemented by independent evaluation whenever feasible. The major effectiveness measures to use for comparison of the drug with the placebo should be the change in odor over the treatment periods (i.e., two segments of crossover) and the subject's odor rating at the end of each treatment period. Other measures, such as changes in the project staff member's ratings and a subjective comparison of treatments by the patient at the end of the study, should also be of help in evaluating effectiveness.

10. *Statistical tests and sample size.* Appropriate statistical tests for crossover designs should be used to establish effectiveness. Sample sizes 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 (e.g., 0.20) of not detecting a significant clinical superiority of the drug over the placebo. The drug company should be prepared to discuss what is meant by a significant clinical superiority.

11. *Number of clinical trials.* Two separate trials, performed by different investigators at different geographical sites, should be conducted. The samples from each of these sites should be representative of the sample population.

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 I, to read as follows:

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

Subpart I—Deodorant Drug Products for Internal Use

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 I—Deodorant Drug Products For Internal Use

§ 357.801 Scope.

(a) An over-the-counter deodorant drug product for internal use in a form suitable for oral administration is generally recognized as safe and effective and is not misbranded if it meets each condition 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.

§ 357.803 Definitions.

As used in this subpart:

(a) *Colostomy.* An external operative opening from the colon.

(b) *Deodorant for internal use.* An ingredient taken internally to render offensive odors less perceptible.

(c) *Ileostomy.* An external operative opening from the ileum.

§ 357.810 Active ingredients for deodorant drug products for internal use. [Reserved]

§ 357.850 Labeling of deodorant drug products for internal use.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a "deodorant for internal use."

(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 phrases:

(1) "A colostomy of ileostomy deodorant."

(2) "An aid to reduce odor from colostomies or ileostomies."

(c) *Other required statement.* The labeling of the product contains the following statement "this product cannot be expected to be effective in the reduction of odor due to faulty personal hygiene."

(d) *Warnings.* [Reserved]

(e) *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. 82-8 Filed 1-4-82; 8:45 am]

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