DEPARTMENT OF HEALTH AND HUMAN SERVICES

21 CFR Part 357

[Docket No. 81N-0064]

RIN 0905-AA06

Deodorant Drug Products for Internal Use for Over-the-Counter Human Use; Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) deodorant drug products for internal use (drug products taken internally to reduce odors arising from conditions such as colostomies, ileostomies, or fecal incontinence) are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on deodorant drug products for internal use that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: May 13, 1991.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of January 5, 1982 (47 FR 512), FDA published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), an advance notice of proposed rulemaking to establish a monograph for OTC deodorant drug products for internal use, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous Internal Drug Products (Miscellaneous Internal Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in this drug class. Interested persons were invited to submit comments by April 5, 1982. Reply comments in response to comments filed in the initial comment period could be submitted by May 5, 1982.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, Rm. 4-62, 5600 Fishers Lane, Rockville, MD 20857, after deletion of a small amount of trade secret information.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC deodorant drug products for internal use was published in the **Federal Register** of June 17, 1985 (50 FR 25162). Interested persons were invited to file by August 16, 1985, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by October 15, 1985. New data could have been submitted until June 17, 1986, and comments on the new data until August 18, 1986. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC deodorant drug products for internal use.

The OTC drug procedural regulations (21 CFR 330.10) now provide that any testing necessary to resolve the safety or effectiveness issues that formerly resulted in a Category III classification, and submission to FDA of the results of that testing or any other data, must be done during the OTC drug rulemaking process before the establishment of a final monograph. Accordingly, FDA is no longer using the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but is using instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III).

As discussed in the proposed regulation for OTC deodorant drug products for internal use, the agency advised that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register.** Therefore, on or after May 13, 1991, no OTC drug product that is subject to the monograph and that contains a nonmonograph condition, i.e., a condition that would cause the drug to be not generally recognized as safe and effective or to be misbranded, may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved new drug application. Further, any OTC drug product subject to this monograph that is repackaged or relabeled after the effective date of the monograph must be in compliance with the monograph regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the monograph at the earliest possible date.

In response to the proposed rule on OTC deodorant drug products for internal use, one drug manufacturer submitted a comment. A copy of the comment received is on public display in the Dockets Management Branch (address above). Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notice published in the **Federal Register** of November 16, 1973 (38 FR 31696), or to additional information that has come to the agency's attention since publication of the notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comment

One comment requested that the agency's proposed oral dosage of 100 to 200 milligrams (mg) daily of chlorophyllin copper complex for adults and children 12 years of age and over be changed to be "100 to 200 mg daily or up to 800 mg daily in divided doses as required." Noting that the normal dosage should be 100 to 200 mg daily, the comment stated that a higher dosage of up to 800 mg may be required in some cases and cited as support three previously submitted studies in which chlorophyllin copper complex was used as an internal deodorant at various dosage levels ranging from 100 to 800 mg daily (Refs. 1, 2, and 3). The comment also noted that the Miscellaneous Internal Panel found chlorophyllin copper complex to be safe up to 800 mg daily in divided doses and that few side effects had been reported at this dosage level (47 FR 512 at 517). The comment stated that the current label dosage for its chlorophyllin copper complex product is one or more tablets daily as required and that the package insert states that one to two tablets three or four times daily may be required initially, followed by a reduction to a maintenance level of one to three tablets daily as required. The comment added that its product has been marketed for

almost 30 years with these directions with few reports of side effects. The comment maintained that the dosage of chlorophyllin copper complex should be revised to provide flexibility for patients to use and for doctors to recommend higher doses than those proposed in the tentative final monograph. The comment concluded that a dosage of up to 800 mg daily is justified based on the product's marketing history, the Miscellaneous Internal Panel's findings that 800 mg of chlorophyllin copper complex is safe, and the submitted references (Refs. 1, 2, and 3).

The agency has reviewed and evaluated the studies referred to by the comment (Refs. 1, 2, and 3) and other available data (Refs. 4, 5, and 6) and concludes that the date are insufficient to support a change in the maximum daily OTC dosage for chlorophyllin copper complex from 200 mg to 800 mg. However, the agency concludes that the data support an increase in dosage of up to 300 mg daily, in divided doses.

In the first study cited by the comment, a group of 22 patients with offensive odors arising from colostomies, ileostomies, and chronically infected surface ulcerations received chlorophyllin copper complex in a tablet form for oral administration (Ref. 1). The study covered a two-year period. The dosage varied in individual cases and ranged from one 100 mg tablet once daily, to two 100 mg tablets three times daily, depending on the nature of the food ingested and the frequency of changing or emptying bags. Placebo substances identical in appearance with the chlorophyll preparations were substituted from time to time, and almost without exception distressing odors reappeared. Odor was satisfactorily eliminated in all cases involving colostomy and ileostomy patients following oral administration of chlorophyllin copper complex tablets. The investigators noted that odor was easier to control in colostomy patients and that, after several weeks, these patients were able to control odor and discharge with irrigations alone, although in many cases they desired the extra protection of the tablets. In this study, three pilonidal cystectomy patients (i.e., patients with chronically infected sacrococcygeal cysts treated by the open wound method) required the larger dose of chlorophyllin copper complex (800 mg) to effectively control the overwhelming odor associated with this condition. The investigators found that an increase to two 100 mg doses four times daily, effectively eliminated the odor with no adverse side effects.

In the second study cited by the comment, 62 geriatric nursing home patients (32 of whom were incontinent and had a foul fecal odor) were given a usual dosage of one 100 mg tablet three times daily for the first 7 to 10 days, and thereafter one 100 mg tablet twice daily for a period of 6 months (Ref. 2). This dosage of chlorophyllin copper complex was found to be at least 85 percent effective in controlling body and fecal odor. No unfavorable side effects were observed.

In the third study cited by the comment, nine patients with urinary and/or fecal incontinence rated as causing "strong odor" were treated with one 100 mg tablet daily for a 30-day period (Ref. 3). Prior to administration of the deodorant, there was a 7-day control period in which evaluations of the ward were made to established a base level against which to compare subsequent progress. The author reported that seven of these patients responded promptly to the treatment and were virtually odorless by the seventh day. Of the two patients who did not respond to one 100 mg tablet daily, one was later given a dosage of two 100 mg tablets per day with the higher dosage effectively controlling the odor.

In the first of three additional studies available to the agency, involving 18 incontinent nursing home patients, it was reported that a rigid schedule of toilet checks and immediate clean up controlled fecal odor but had little effect on urine odors that pervaded the floor (Ref. 4). Nine of the 18 patients were given one tablet per day containing 100 mg of chlorophyllin while the other 9 were continued on the other rigid clean-up schedule. The author reported that within two days the odor was noticeablely reduced and within seven days the urinary odor was completely eliminated. The author further reported that during the following 2-year period, the tablets were used by the nine patients in the study and other incontinent patients and there was neither any diminution in the effectiveness of the odor control nor the appearance of any undesirable side effects.

In the second additional study, 15 ostomy patients (7 ileostomy, 7 colostomy, and 1 cecostomy) took the recommended initial dosage of chlorophyllin copper complex of one 100 mg tablet twice daily; but patients were advised to increase the dosage to 3 or 4 tablets a day or to reduce the dosage to 1 per day at their own discretion depending on the control of odor (Ref. 5). The investigator reported that excellent results were obtained in 14 out of 15 cases with little difference in effect between 2 or 3 100 mg tablets daily; however, in 2 of these patients some odor reappeared when the daily dosage was decreased from three to two 100 mg tablets.

The one unsuccessful case in which odor was not controlled involved a colostomy patient who also developed excess gas and diarrhea while taking the tablets. The symptoms disappeared when the dosage was discontinued. No definite toxicity or side reactions were encountered, although in one patient, a dosage of two 100 mg tablets daily produced cramps. The cramps were eliminated when the dosage was reduced to one 100 mg tablet daily.

In the third additional study, which was conducted over a 2-year period, 20 female mental patients were given 100 mg of chlorophyllin per day (Ref. 6). Seventy-five percent of the patients were treated for malodorous odor resulting from surface lesions, while the remaining 25 percent included incontinent or bed-pan patients with fecal and/or urine incontinence. Within 5 to 6 days, the odor was almost completely gone. Results were reported to be uniformly good over the entire study period. There were no side effects other than an occasional, mild diarrhea.

After reevaluating the above studies and other available data, the agency has determined there are insufficient data demonstrating that a dosage above 300 mg is generally necessary or used to effectvely control odor in ostomy or fecal incontinent patients. Although three pilonidal cystectomy patients were given up to four 200 mg doses of chlorophyllin copper complex daily in one of the cited studies (Ref. 1), there is no indication that this dosage was necessary for the ostomy and incontinent patients included in the study. Other studies indicate that satisfactory results in colostomy patients have been achieved with lower doses ranging from 56 to 112 mg per day (Refs. 7 and 8). The agency has not received any other data that support the regular use of chlorophyllin copper complex in a dosage of above 300 mg up to 800 mg per day. The agency has determined that the available data indicate that, in most cases involving odors due to colostomies, ileostomies, and fecal incontinence, most patients respond well to one or two 100 mg doses of chlorophyllin copper complex daily. However, some of the studies indicate that 300 mg daily is needed in some cases to effectively control the odor (Refs. 2 and 5). Therefore, in this final monograph, the agency is revising the directions for chlorophyllin copper

complex to include a dose of up to 300 mg as follows: "Adults and children 12 years of age and over: Oral dosage is 100 to 200 milligrams daily in divided doses as required. If odor is not controlled, take up to an additional 100 milligrams daily in divided doses as required. The smallest effective dose should be used. Do not exceed 300 milligrams daily. Children under 12 years of age: consult a doctor."

Additionally, based on the side effects that occurred (Refs. 5 and 6), the agency is adding a warning for products containing chlorophyllin copper complex to the final monograph that states: "If cramps or diarrhea occurs, reduce the dosage. If symptoms persist, consult your doctor." This warning is also consistent with the revised directions to use the smallest effective dose of the product.

The agency's detailed comments and evaluations on the data are on file in the Dockets Management Branch (Ref. 9).

References

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

(2) Young R.W., and J.S. Beregi, Jr., "Use of Chlorophyllin in the Care of Geriatric Patients," *Journal of the American Geriatrics Society*, 28:46–47, 1980.

(3) Noonan, L., "Summary of Derifil Tablets Trial," unpublished study, Rockland State Hospital, Orangeburg, NY, April 1972, contained in OTC volume 170014 (Exhibit Y), Docket No. 81N–0064, Dockets Management Branch.

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

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

(6) O'Connell, I.O., "A Useful Adjunct For Odor Control In Malodorous Surface Lesions and Incontinence," *Journal of the Central Islip State Hospital*, 1:23–26, 1967–1968.

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

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

(9) Letter from W.E. Gilbertson, FDA, to H. Wagner, Rystan Company, Inc., coded LET4, Docket No. 81N–0064, Dockets Management Branch.

II. Summary of Significant Changes From the Proposed Rule

1. In the tentative final monograph published in the **Federal Register** of June 17, 1985, (50 FR 25162 at 25167) at § 357.850(b)(2)(ii), the agency proposed the indication "an aid to reduce fecal or urinary odor due to incontinence" for chlorophyllin copper complex when used in the dosage range of 100 to 200 mg daily. However, since the publication of the tentative final monograph, the agency has become aware of new data suggesting that chlorophyllin copper complex may not be effective for the reduction of odor due to urinary incontinence.

In a 5-week randomized, double-blind, crossover, placebo-controlled study, Nahata, Slencsak, and Kamp (Ref. 1) evaluated the effect of chlorophyllin on urinary odor due to incontinence. Twenty incontinent geriatric patients having indwelling Foley catheters were given either 100 mg chlorophyllin or placebo once daily for two weeks. The third week served as a washout period, after which the patients were placed on another regimen in a crossover fashion, for the next two weeks. The intensity of urinary odor was measured by using a 10-centimeter visual analog scale with 0 representing no odor and 10 representing maximum, severe, terrible odor. Urine samples were collected, covered, and taken to a room with no odor. Urinary odor intensity was measured on alternate days during the first week (weeks 1 and 4) and daily during the second week (weeks 2 and 5) of chlorophyllin and placebo administration. Statistical analysis of the data using analysis of variance (ANOVA) showed no significant difference (p greater than 0.05) in the mean intensity of urinary odor during chlorophyllin, washout, and placebo periods. None of the patients exhibited any adverse effects during the entire study period. The results of this study suggest that chlorophyllin in a dosage of 100 mg daily for two weeks may not be effective in incontinent geriatric patients with mild to moderate urinary odor.

Of the studies previously available to the agency and cited in the tentative final monograph (50 FR 25162 at 25164), only one uncontrolled study by Dory (see Part I above) evaluated the effectiveness of chlorophyllin in a dosage of 100 mg per day for the reduction of the odor of urinary incontinence alone (Ref. 2). In the Dory study only nine patients received chlorophyllin and in the other submitted studies, reduction of odors of fecal and urinary incontinence was not treated separately. No data have been submitted to demonstrate that chlorophyllin is metabolized from the gastrointestinal tract and is made available for excretion by the urinary system. Therefore, because of conflicting and insufficient data, labeling claims for reduction of odor due to urinary incontinence are not being included in this final monograph. Data from well-controlled clinical trials are necessary to support the use of chlorophyllin copper complex for reduction of odors due to urinary incontinence.

Additionally, the agency has revised the definition of deodorants for internal use in this final monograph to be consistent with the indication for use included in the monograph. (See § 357.803(b) below.)

References

(1) Nahata, M. C., C. A. Slencsak, and J. Kamp, "Effect of Chlorophyllin on Urinary Odor in Incontinent Geriatric Patients", *Drug Intelligence and Clinical Pharmacy*, 17:732–734, 1983).

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

2. The agency has added a warning related to cramps and diarrhea for products containing chlorophyllin copper complex. (See Part I above.)

3. The agency has revised the directions in § 357.850(d)(2) for chlorophyllin copper complex as follows: *For products containing chlorophyllin copper complex identified in § 357.810(b).* Adults and children 12 years of age and over: Oral dosage is 100 to 200 milligrams daily in divided doses as required. If odor is not controlled, take up to an additional 100 milligrams daily in divided doses as required. The smallest effective dose should be used. Do not exceed 300 milligrams daily. Children under 12 years of age: consult a doctor. (See Part I above.)

III. The Agency's Final Conclusions on OTC Deodorant Drug Products for Internal Use

Based on the available evidence, the agency is issuing a final monograph establishing conditions under which OTC deodorant drug products for internal use are generally recognized as safe and effective and not misbranded. Specifically, the agency has determined that the ingredients bismuth subgallate and chlorophyllin copper complex are generally recognized as safe and effective for use as an aid to reduce odor from a colostomy or ileostomy.

The agency is not aware of adequate data demonstrating the safety and effectiveness of any other ingredients as OTC deodorant drug products for internal use. Therefore all other ingredients, including but not limited to activated charcoal, are considered nonmonograph conditions for use as OTC deodorant drug products for internal use. Any drug product marketed as an OTC deodorant for internal use that is not in conformance with the monograph (21 CFR Part 357, Subpart I) may be considered a new drug within

the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352) and may not be marketed for this use unless it is the subject of an approved new drug application (NDA). An appropriate citizen petition to amend the monograph may also be submitted under 21 CFR 10.30.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (50 FR 25162 at 25166). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that not one of these rules, including this final rule for OTC deodorant drug products for internal use, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act (Pub. L. 96-354). That assessment included a discretionary regulatory flexibility analysis in the event that an individual rule might impose an unusual or disproportionate impact on small entities. However, this particular rulemaking for OTC deodorant drug products for internal use is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

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

List of Subjects in 21 CFR Part 357

Internal deodorant drug products, Labeling, Over-the-counter drugs, Recordkeeping and reporting requirements.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, subchapter D of chapter I of title 21 of the Code of Federal Regulations is amended in part 357 as follows:

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

1. The authority citation for 21 CFR Part 357 continues to read as follows:

Authority: Secs. 201, 501, 502, 503, 505, 510, 701 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 351, 352, 353, 355, 360, 371).

2. Part 357 is amended by adding new Subpart H and reserving it, and by adding new Subpart I consisting of §§ 357.801 to 357.850 to read as follows:

Subpart H—[Reserved]

Subpart I—Deodorant Drug Products for Internal Use

Sec.

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 of the colon.

(b) *Deodorant for internal use.* An ingredient taken internally to reduce odors arising from conditions such as colostomies, ileostomies, or fecal incontinence.

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

(d) *Incontinence.* An inability to retain urine or feces.

§ 357.810 Active ingredients for deodorant drug products for internal use.

The active ingredient of the product consists of either of the following when used within the dosage limits established for each ingredient in § 357.850(d):

(a) Bismuth subgallate.

(b) Chlorophyllin copper complex.

§ 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" or as a "colostomy or ileostomy deodorant."

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in paragraph (b) of this section as appropriate. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in paragraph (b) of this section may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) *For products containing bismuth subgallate identified in § 357.810(a).* "An aid to reduce odor from a colostomy or ileostomy."

(2) *For products containing chlorophyllin copper complex identified in § 357.810(b).* (i) "An aid to reduce odor from a colostomy or ileostomy."

(ii) "An aid to reduce fecal odor due to incontinence."

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings": (1) *For products containing chlorophyllin copper complex identified in § 357.810(b).* (i) "If cramps or diarrhea occurs, reduce the dosage. If symptoms persist, consult your doctor."

(ii) The warning required by § 330.1(g) of this chapter concerning overdose is not required on products containing chlorophyllin copper complex identified in § 357.810(b).

(2) [Reserved]

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions."

(1) *For products containing bismuth subgallate identified in § 357.810(a).* Adults and children 12 years of age and over: Oral dosage is 200 to 400 milligrams up to 4 times daily. Children under 12 years of age: consult a doctor.

(2) *For products containing chlorophyllin copper complex identified in § 357.810(b).* Adults and children 12 years of age and over: Oral dosage is 100 to 200 milligrams daily in divided doses as required. If odor is not controlled, take up to an additional 100 milligrams daily in divided doses as

required. The smallest effective dose should be used. Do not exceed 300 milligrams daily. Children under 12 years of age: consult a doctor.

Dated: March 27, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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