carcinogenesis *in vitro*. *Carcinogenesis*, Vol. 6, No. 6, pp. 859–864.

41. *Microwave News* (1985). Polish epidemiology study links RF/MW exposures to cancer. *Microwave News*, Vol. V, No. 2, March, p. 1.

42. ONR (1984). Electromagnetic waves and neurobehavioral function: an international workshop. ONR London Conference Report, C–6–84, October 19, 1984. Office of Naval Research.

43. Kues, H.A., *et al.* (1985). Effects of 2.45–GHz microwaves on primate corneal endothelium. *Bioelectromagnetics*, Vol. 6, No. 2, pp. 177–188.

44. ACGIH (1983). Threshold limit values for chemical substances and physical agents in the work environment with intended changes for 1983–84. American Conference of Governmental Industrial Hygienists, 6500 Glenway Ave., Bldg. D–5, Cincinnati, Ohio 45211.

45. Ellis, F.P. (1972). Mortality from heat illness and heat-aggravated illness in the United States. *Environmental Research*, Vol. 5, pp. 1–58.

46. Nutrition Foundation (1982). A proposed food safety evaluation process. Food Safety Council, 888 7th St., N.W., Washington, DC 20006, June.

47. National Academy of Sciences (1977). Drinking water and health, part I. A report of the Safe Drinking Water Committee, Advisory Center on Toxicology, Assembly of Life Sciences, National Research Council, Washington.

48. Dourson, M.L. and J.F. Stara (1983). Regulatory history and experimental support of uncertainty (safety) factors. *Regulatory Tox. and Pharm.*, Vol. 3, pp. 224–238.

49. EPA (1983). Guidelines for performing regulatory impact analyses. Office of Policy Analysis. EPA report, EPA 230–01–84–003, December.

50. Christian, M.S., *et al.*, Ed. (1983). Assessment of reproductive and teratogenic hazards. Advances in Modern Environmental Toxicology, Vol. III. Princeton Scientific Publishers, Inc., Princeton, New Jersey.

51. Gandhi, O.P., *et al.* (1985). Likelihood of high rates of energy deposition in the human legs at the ANSI recommended 3–30 MHz RF safety limits. *Proc. IEEE*, Vol. 73, No. 6, June, pp. 1145–1147.

52. Berman, E., *et al.* (1984). Growth and development of mice offspring after irradiation *in utero* with 2,450 MHz microwaves. *Teratology*, Vol. 30, pp. 393–402.

53. EPA (1985). Radiofrequency radiation measurement survey, Honolulu, Hawaii, May 14–25, 1984. Office of Radiation Programs.

54. Deno, D.W. (1974). Calculating electrostatic effects of overhead transmission lines. *IEEE Trans. Power Apparatus and Systems*, Vol. PAG–3, pp. 1458–1466.

55. Banks, R.S., C.M. Kannianen, and R.D. Clark (1977). Public health and safety effects of high-voltage overhead transmission lines: An analysis for the Minnesota Environmental Quality Board, Minnesota Department of Health, Division of Environmental Health, Minneapolis, MN, October.

56. Tell, R.A., and E.D. Mantiply, C.H. Durney, and H. Massoudi, Electric and magnetic field intensities and associated induced currents in man in close proximity to a 50 kW AM standard broadcast station. In Program and Abstracts, United States National Committee, International Union of Radio Science, and Bioelectromagnetics Symposium, June 18–22, 1979, Seattle, Washington, p. 360. To be submitted for publication to *IEEE Transactions on Broadcasting*.

57. Dalziel, C.F., E. Ogden, and C.E. Abbott (1943). Effect of frequency on let-go currents. *Electrical Engineering Transactions*, Vol. 62, December, pp. 745–749.

58. Dalziel, C.F. and T.H. Mansfield (1950). Effect of frequency on perception currents. *AIEE Transactions*, Vol. 69, pt. II, pp. 1162–1168.

59. NIOSH (1985). Radiofrequency/microwave occupational exposure standard and rationale, external review draft. National Institute for Occupational Safety and Health, U.S. Department of Health and Human Services.

60. ANSI (1973). American National Standard techniques and instrumentation for the measurements of potentially hazardous electromagnetic radiation at microwave frequencies. American National Standards Institute C95.3–1973.

61. Tell, R.A. (1983). Instrumentation for measurement of electromagnetic fields: equipment, calibrations, and selected applications. In Biological Effects and Dosimetry of Nonionizing Radiation, ed. M. Grandolfo, S.M. Michaelson, and A. Rindi. Plenum Press, New York, pp. 95–162.

62. ECAC (1982). Support to the Environmental Protection Agency nonionizing radiation source analysis. Electromagnetic Compatibility Analysis Center, Report No. ECAC–CR–82–093, September.

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federal register

Wednesday
July 30, 1986

Part III

Department of Health and Human Services

Food and Drug Administration

21 CFR Part 331

Antacid Drug Products for Over-the-Counter Human Use; Proposed Rules

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 331

[Docket No. 85N-0049]

Antacid Drug Products for Over-the-Counter Human Use; Proposed Amendment of Antacid Monograph

AGENCY: Food and Drug Administration.

ACTION: Proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking that would amend the final monograph for over-the-counter (OTC) antacid drug products to require that all antacid drug products contain the statement "Antacids may interact with certain prescription drugs. If you are presently taking a prescription drug, do not take this product without checking with your physician." FDA is issuing this notice of proposed rulemaking after considering public comments to a prior proposal (see the **Federal Register** of October 19, 1979; 44 FR 60328) and a citizen petition (Docket No. 82P-0360/CP) that requested additional labeling information to be included on OTC antacid drug products. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATE: Written comments or objections by September 29, 1986.

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

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of June 4, 1974 (39 FR 19862), FDA issued a final monograph for OTC antacid drug products (21 CFR Part 331). Under § 331.30(d)(1), the labeling of OTC aluminum-containing antacid drug products is required to contain the drug interaction precaution "Do not take this product if you are presently taking a prescription antibiotic drug containing any form of tetracycline." In the **Federal Register** of October 19, 1979 (44 FR 60328), the agency proposed to amend the antacid monograph to require that this drug interaction precaution also be included on the labeling of antacid drug products containing calcium or magnesium. The proposed amendment would have also required the following additional statement as part of the drug interaction precaution: "If you are not sure whether or not you are taking a tetracycline product, contact your physician or pharmacist." Interested persons were invited to file written comments to the proposed amendment on or before December 18, 1979.

In response to the notice of proposed rulemaking, five manufacturers, one trade association, one citizen's group, and one pharmaceutical association submitted comments. A number of the comments questioned the necessity and desirability of the second statement of the proposed warning. One comment questioned FDA's general policy with respect to OTC drug-prescription drug interaction precaution statements, in particular whether such statements should appear in prescription labeling rather than OTC drug labeling. Another comment urged that the proposed warning be limited to instances involving concurrent (simultaneous) ingestion of the antacids and tetracycline. One comment concurred with the proposed warning, but suggested the FDA consider expanding the warning to include prescription drug products other than tetracycline, or broadening it to include other products containing aluminum, calcium, or magnesium. Copies of the comments received are on public display in the Dockets Management Branch.

On November 15, 1982, FDA received a petition (Docket No. 82P-0360/CP) requesting, among other things, that the labeling of OTC antacid drug products include a precaution concerning the interaction between antacids and the prescription drug digoxin. In a letter dated August 23, 1983, the agency responded to the petition and stated that FDA would initiate the necessary action to implement the petitioner's request with respect to the drug interaction precaution.

After considering the comments to the October 19, 1979 proposed rule (44 FR 60328) and the petition received on November 15, 1982 (Docket No. 82P-0360/CP), the agency believes it is necessary to clarify its policy with respect to drug interaction precaution statements in the labeling of OTC drug products.

The agency's general approach to drug interaction labeling on OTC drug products was discussed in the **Federal Register** of June 4, 1974 (39 FR 19880). In the interest of providing fully informative labeling to the consumer, the agency stated "that the proper way to handle possible drug interactions is to require that the labeling [of OTC drug products] include a separate section headed 'Drug Interaction Precautions,' stating the specific or general interaction problem involved with that particular OTC drug. . . . The same format will be used for other specific drug interactions found to exist in other monographs. Where known drug interactions exist but are not limited to a specific drug, the precaution statement shall be phrased in terms of general drug categories. . . ." The agency has been operating under this general policy since it was stated in the June 4, 1974 **Federal Register**.

However, in light of the comments made to the October 19, 1979 proposed rule, the agency believes it is necessary to expand its policy as follows:

1. In general, the agency believes that when an interaction between a prescription drug and an OTC drug is significant enough to be included in the approved labeling of the prescription drug product, a similar corresponding warning should be included in the labeling of the OTC drug product.

This general policy may not apply when the known prescription-OTC drug interaction cited in the prescription drug labeling affects only a limited portion of the total population taking the prescription drug. For example, the labeling for the prescription drug dexamethasone includes a statement advising that aspirin should be used cautiously in conjunction with corticosteroids in hypoprothrombinemia. Conceivably, only a small subset of the population taking dexamethasone would have a hypoprothrombinemic condition and, therefore, the label warning may not be necessary on OTC aspirin-containing drug products.

2. Consistent with the June 4, 1974 **Federal Register** statements, in those cases where the known interactions are not limited to specific drugs and involve numerous drugs or entire drug categories, the statement would be phrased in terms of general drug categories. For example, if a significant number of prescription drugs are known to interact with an OTC drug, the interaction warning may need to be a general "prescription drug" warning rather than a listing of all possible prescription drugs likely to cause interactions.

3. Where interactions are known to exist between OTC drug products and are recognized as being significant, all of the OTC drug products involved should include the drug interaction precaution.

In the case of antacid drug products, the interaction between aluminum, calcium, or magnesium antacids and tetracycline is the most frequently reported. However, the agency is aware

of data in the literature indicating that the entire class of antacides, due to pH-related and other mechanisms, interacts with a number of other drugs (Refs. 1 through 6). Many of the interactions result from elevation of the pH of the stomach contents produced by the antacids, which may in turn affect the rate of absorption of a number of drugs. In some cases the interaction may be beneficial, i.e., the drug may be absorbed faster and get to the site of action quicker. For example, the rate of absorption of salicylates, indomethacin, naproxen, pseudoephedrine, sulfadiazine, and levodopa is increased by elevated gastric pH.

In other cases, the rate of absorption may be delayed, thereby reducing efficacy of the drug. For example, the efficacy of tetracycline, digoxin, phenytoin, chlorpromazine, and isoniazid is reduced because of reduced absorption of the drugs. Aluminum hydroxide delays gastric emptying, thereby slowing the rate of absorption of indomethacin, dicumarol, isoniazid, barbiturates, and some benzodiazepines. In addition, aluminum hydroxide can adsorb and decrease the bioavailability of propranolol, antimuscarinic drugs, digoxin, tetracyclines, chlorpromazine, and sulfadiazine. Likewise, magnesium trisilicate interferes with the bioavailability of digoxin, certain benzodiazepines, phenothiazines, and antimuscarinic drugs. Antacids that increase urinary pH can delay the elimination and elevate the blood levels of quinidine and amphetamines.

Because of the number of significant interactions that can occur between antacids and prescription drugs, the agency is proposing the following drug interaction precaution for inclusion in the labeling of all OTC antacid drug products: "Antacids may interact with certain prescription drugs. If you are presently taking a prescription drug, do not take this product without checking with your physician." This statement would replace the current drug interaction precaution statement required by 21 CFR 331.30(d)(1). The statement proposed here would also replace the wording proposed in the **Federal Register** of October 19, 1979 (44 FR 60328). Elsewhere in this issue of the **Federal Register**, the agency is withdrawing the proposed rule of October 19, 1979.

In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This document proposes that that option be added to the final monograph for OTC antacid drug products.

References

(1) "Evaluation of Drug Interactions," 2d Ed., American Pharmaceutical Association, Washington, 1976.

(2) Hurwitz, A., "Antacid Therapy and Drug Kinetics," *Clinical Pharmacokinetics*, 2:269–280, 1977.

(3) Romankiewicz, J.A., "Effects of Antacids on Gastrointestinal Absorption of Drugs," *Primary Care*, 3:537–550, 1976.

(4) Harvey, S.C., "Gastrict Antacids and Digestants" *in* "The Pharmacological Basis of Therapeutics," 6th Ed., edited by L.S. Goodman, A. Gilman, and A.G. Gilman, Macmillan Publishing Co., Inc., New York, pp. 988–991, 1980.

(5) Garnett, W.R., "Antacid Products" *in* "Handbook of Nonprescription Drugs," 7th Ed., American Pharmaceutical Association, Washington, pp. 34–37, 1982.

(6) Hartshorn, E.A., "Drug Interactions Update 1982," American Society of Hospital Pharmacists, Bethesda, MD, 1983.

Because this proposal relates only to warnings for OTC antacid drug products, the changes in the "exclusivity" policy that were recently published in the **Federal Register** of May 1, 1986 (51 FR 16258) do not apply to this document.

The agency advises that any final rule resulting from this proposed rule will be effective 12 months after its date of publication in the **Federal Register**. On or after that date, OTC drug products that are not in compliance may not be initially introduced or initially delivered for introduction into interstate commerce unless they are the subject of an approved new drug application (NDA). Further, any OTC drug products subject to the rule that are repackaged or relabeled after the effective date of the rule must be in compliance with the rule 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 rule at the earliest possible date.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC antacid drug products, is a major rule.

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

The agency invites public comment regarding any substantial or significant economic impact that this rulemaking would have on OTC antacid drug products. Comments regarding the impact of this rulemaking on OTC antacid drug products should be accompanied by appropriate documentation.

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

Interested persons may, on or before September 29, 1986, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments or objections. Three copies of all comments or objections are to be submitted, except that individuals may submit one copy. Comments and objections are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments and objections may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

List of Subjects in 21 CFR Part 331

OTC drugs, Antacid drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the

Administrative Procedure Act, it is proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended in Part 331 as follows:

PART 331—ANTACID PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

1. The authority citation for Part 331 continues to read as follows:

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

2. In § 331.30 by revising paragraph (d) and adding new paragraph (h) to read as follows:

§ 331.30 Labeling of antacid products.

* * * * *

(d) *Drug interaction precautions.* The labeling of the product contains the following statement under the heading "Drug Interaction Precautions": "Antacids may interact with certain prescription drugs. If you are presently taking a prescription drug, do not take this product without checking with your physician."

* * * * *

(h) The word "doctor" may be substituted for the word "physician" in any of the labeling statements in this section.

Dated: May 3, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 86–17038 Filed 7–29–86; 8:45 am]

BILLING CODE 4160–01–M

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21 CFR Part 331

[Docket No. 79N–0152]

Antacid Drug Products for Over-the-Counter Human Use; Withdrawal of Proposed Rule

AGENCY: Food and Drug Administration.

ACTION: Withdrawal of proposed rule.

SUMMARY: The Food and Drug Administration (FDA) is withdrawing a proposed rule that would have required over-the-counter (OTC) antacid drug products containing calcium and magnesium to contain a precautionary statement. Elsewhere in this issue of the **Federal Register,** FDA is proposing a revised drug interaction precaution for all OTC antacid drug products. That proposal supersedes the proposal being withdrawn.

EFFECTIVE DATE: July 30, 1986.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drugs and Biologics (HFN–210), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301–295–8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of October 19, 1979 (44 FR 60328), FDA published a proposal to amend the monograph for OTC antacid drug products (21 CFR Part 331) to require a tetracycline drug interaction precaution statement on the labeling of calcium- and magnesium-containing OTC antacid drug products. The statement previously had been required only for aluminum-containing OTC antacid drug products. Elsewhere in this issue of the **Federal Register,** the agency is proposing an amendment to the monograph for OTC antacid drug products to require a prescription drug interaction precaution for all OTC antacid drug products. The new proposal supersedes the October 19, 1979 proposal, which is being withdrawn.

List of Subjects in 21 CFR Part 331

OTC drugs; Antacid drug products.

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)), under 21 CFR 5.11, and under 21 CFR 10.40(c), the proposed rule published in the **Federal Register** of October 19, 1979 (44 FR 60328) is withdrawn effective July 30, 1986.

Dated: May 3, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

[FR Doc. 86–17039 Filed 7–29–86; 8:45 a.m.]

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federal register

Wednesday
July 30, 1986

Part IV

Department of Health and Human Services

Food and Drug Administration

21 CFR Parts 348 and 358

External Analgesic Drug Products for Over-the-Counter Human Use; Amendment to Tentative Final Monograph and Dandruff, Seborrheic Dermatitis, and Psoriasis Drug Products for Over-the-Counter Human Use; Tentative Final Monograph; Further Notice of Proposed Rulemaking and Notice of Proposed Rulemaking

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 358

[Docket No. 82N-0214]

Dandruff, Seborrheic Dermatitis, and Psoriasis Drug Products for Over-the-Counter Human Use; Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Notice of proposed rulemaking.

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

DATES: Written comments, objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by September 29, 1986. New data by July 30, 1987. Comments on the new data by September 30, 1987. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by November 28, 1986.

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

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 3, 1982 (47 FR 54646), 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 dandruff, seborrheic determatitis, and psoriasis drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by March 3, 1983. Reply comments in response to comments filed in the initial comment period could be submitted by April 4, 1983.

In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5762), the agency advised that it had extended the comment period until April 4, 1983, and the reply comment period to May 4, 1983, on the advance notice of proposed rulemaking for OTC dandruff, seborrheic dermatitis, and psoriasis drug products to allow for consideration of additional data and information.

In accordance with § 330.10(a)(10), the data and information considered by the Panel were put on public display in the Dockets Management Branch (HFA-305), Food and Drug Administration (address above), after deletion of a small amount of trade secret information.

In response to the advance notice of proposed rulemaking, 11 manufacturers, 4 trade associations, 6 universities and foundations, and 5 health professionals submitted comments. Copies of the comments received are on public display in the Dockets Management Branch.

In order to conform to terminology used in the OTC drug review regulations (21 CFR 330.10), the present document is designated as a "tentative final monograph." Its legal status, however, is that of a proposed rule. In this tentative final monograph (proposed rule) to establish Subpart H of Part 358 (21 CFR Part 358 Subpart H), FDA states for the first time its position on the establishment of a monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products. Final agency action on this matter will occur with the publication at a future date of a final monograph, which will be a final rule establishing a monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products.

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

The OTC procedural regulations (21 CFR 330.10) 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 will no longer use the terms "Category I" (generally recognized as safe and effective and not misbranded), "Category II" (not generally recognized as safe and effective or misbranded), and "Category III" (available data are insufficient to classify as safe and effective, and further testing is required) at the final monograph stage, but will use instead the terms "monograph conditions" (old Category I) and "nonmonograph conditions" (old Categories II and III). This document retains the concepts of Categories I, II, and III at the tentative final monograph stage.

The agency advises that the conditions under which the drug products that are subject to this monograph would be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication of the final monograph in the **Federal Register.** On or after that date, no OTC drug 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 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.

If the agency determines that any labeling for a condition included in the final monograph should be implemented sooner than the 12-month effective date, a shorter deadline may be established. Similarly, if a safety problem is identified for a particular nonmonograph condition, a shorter deadline may be set

for removal of that condition from OTC drug products.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data notices published in the Federal Register of November 16, 1973 (38 FR 31697) and August 27, 1975 (40 FR 38179) or to additional information that has come to the agency's attention since publication of the advance notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Tentative Conclusions on the Comments

A. General Comments.

1. One comment urged that the agency recognize the legal status of the monographs issued under the OTC drug review as interpretive rather than substantive regulations.

The agency addressed this issue in paragraphs 85 through 91 of the preamble to the procedures for classification of OTC drug products, published in the Federal Register of May 11, 1972 (37 FR 9464) and in paragraph 3 of the preamble to the tentative final monograph for antacid drug products, published in the Federal Register of November 12, 1973 (38 FR 31260). FDA reaffirms the conclusions stated there. Subsequent court decisions have confirmed the agency's authority to issue substantive regulations by rulemaking. See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–98 (2d Cir. 1975) and *National Association of Pharmaceutical Manufacturers* v. *FDA*, 487 F. Supp. 412 (S.D.N.Y., 1980), *aff'd*, 637 F.2d 887 (2d Cir. 1981).

2. Noting the Panel's discussion of the microbiology of dandruff and the Panel's conclusion that there is not a definite correlation between the presence of the yeast *Pityrosporum ovale (P. Ovale)* and the development of dandruff (47 FR 54653), one comment cited four articles (Refs. 1 through 4) which were not available to the Panel and which add additional information for consideration.

The agency has reviewed the articles and determined that they offer no reason for the agency to disagree with the Panel's conclusion. Imokawa, Shimizo, and Okamoto (Ref. 1) reported that the use of zinc pyrithione produced a decrease in *P. ovale* corresponding to a reduction in dandruff, but that in the absence of treatment, dandruff returned even though the reduction in *P. ovale* persisted.

Idson (Ref. 2) states that "antidandruff agents owe their success to further qualities than only antimicrobial properties." Aron-Brunetiere, Dompmartin, and Drouhet (Ref. 3) reported that while their study would seem to establish a causal relationship between fungal infestation and dandruff, their results were not conclusive.

Belew (Ref. 4) theorized that there is a possible pathogenic sequence by which *P. ovale* and certain other yeasts could activate the body's immune system, but that the association of these microbial activators with scaling disorders in humans merits future research and consideration.

The agency concurs with the Panel that although there may be an association between the presence of *P. ovale* and dandruff, a definitive correlation has not been established. The Panel recommended that antimicrobial agents be judged on their own merit with respect to control of dandruff (47 FR 54654). The agency concurs. If such agents are shown in well-controlled double-blind clinical studies to be effective in controlling dandruff and are recognized as safe for OTC use, they will be placed in Category I. Such classification should not itself be taken as proof of any particular causal relationship in the treatment of dandruff, however, because an ingredient may be capable of acting in more than one therapeutic manner. For example, an antimicrobial might also have keratolytic or cytostatic properties. (See 47 FR 54654.)

References

(1) Imokawa, G., H. Shimizo, and K. Okamoto, "Antimicrobial Effect of Zinc Pyrithione," *Journal of the Society of Cosmetic Chemists*, 33:27–37, 1982.

(2) Idson, B., "Laboratory and Clinical Evaluation of Antidandruff Preparations," *Journal of the Society of Cosmetic Chemists*, 24:395–398, 1973.

(3) Aron-Brunetiere, R., D. Dompmartin, and E. Drouhet, "Treatment of Pityriasis Capitis (Dandruff) with Econazole Nitrate," *Acta Dermatovener* (Stockholm), 57:77–80, 1977.

(4) Belew, P., "Sabouraud and Pivolta Were Right—Seborrheic Dermatitis is Microbial," *Cosmetics and Toiletries*, 96:25–28, 1981.

3. One comment contended that shampoo and other hair care products represented only to remove loose flakes of dandruff are cosmetics, not drugs, and are not subject to this rulemaking. Citing statements in two letters issued by the agency (Refs. 1 and 2) and FDA's Compliance Program Guidance Manual for fiscal year 1980 (Ref. 3), the comment contented that mere use of the word "dandruff" in the context of a truthful label claim that a cosmetic shampoo or other hair care product will "remove loose flakes of dandruff" from the hair cannot convert the product to a drug. The comment requested that the monograph for OTC dandruff products be modified to include the statement "This monograph does not apply to a shampoo or other hair care product that is represented, insofar as dandruff is concerned, solely to clean the hair and scalp of loose dandruff scales or flakes. Such a product is subject to regulation only as a cosmetic and not a drug."

A reply comment disagreed strongly with the above comment, expressing the opinion that agency officials were incorrect in the cited letters which supported use of the term "dandruff" in cosmetic labeling. This reply comment stated that FDA's 1983 Compliance Program Guidance Manual (Ref. 4) "makes no reference to dandruff and may be properly considered as a revocation of the earlier comment." This comment pointed out that no medical authority has been cited to support the use of the term "dandruff" in cosmetic products.

A second reply comment restated and supported the original comment's arguments that although claims for the "prevention" or "control" of dandruff are drug claims, claims that merely refer to "washing away loose flakes of dandruff" are mere cosmetic claims. This reply comment went on to point out that the first reply comment cited no authority in disagreeing with the letters by agency officials (Refs. 1 and 2) cited in the original comment. This reply comment maintained that no change in agency position (Ref. 3) on the cosmetic/drug status of the term "dandruff" was suggested or implied by the "silence" on the term "dandruff" in the 1983 manual.

The agency agrees with the original comment that the mere use of the word "dandruff" does not automatically render a shampoo or other hair care product subject to regulation as a drug. The Federal Food, Drug, and Cosmetic Act defines a "drug" as an article "intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease . . . (or) intended to affect the structure or any function of the body. . . . (See 21 U.S.C. 321(g)(1) (B) and (C).) A "cosmetic," on the other hand, is defined as an article intended to be "applied to the human body . . . for cleansing, beautifying, promoting attractiveness, or altering the appearance." (See 21 U.S.C. 321(i)(1).) The product's intended use, therefore, determines whether it is a "drug," a "cosmetic," or both. This intended use may be inferred from the product's labeling, promotional material, advertising, and any other relevant factor. See, e.g., *National Nutritional Foods Association* v. *Mathews*, 557 F.2d

325, 334 (2d Cir. 1977). When the use of the term "dandruff" deals only with appearance and not with the treatment or prevention of the underlying disease condition, as in the context that a product removes loose flakes of dandruff or cleans the hair of dandruff flakes or scales, the product is cosmetic in nature. This position is clearly and correctly stated by the agency in the letters cited by the original comment (Refs. 1 and 2).

Any use of the term dandruff that would make or imply a claim for the prevention, control, or treatment of dandruff beyond the simple mechanical removal of flakes and scales would, of course, render the product a drug. Examples of claims that would cause a hair care product to become a drug include terms such as "antidandruff," "dandruff control shampoo," "dandruff treatment," or "prevents dandruff." The agency further concludes that the differences between drug and cosmetic claims are sufficiently clear that the statement requested by the first comment is unnecessary.

References

(1) Letter from E. G. Seibert, FDA, October 29, 1980, in OTC Volume 16MTFM.

(2) Letter from R. C. Wetherell, Jr., FDA, to Senator J. K. Javits, May 10, 1979, in OTC Volume 16MTFM.

(3) FDA Compliance Program Guidance Manual, Program 7329.001, Chapter 29, Cosmetics, 1980, copy included in OTC Volume 16MTFM.

(4) FDA Compliance Program Guidance Manual, Program 7329.001, Chapter 29, Cosmetics, 1983, copy included in OTC Volume 16MTFM.

4. One comment stated that the Panel's recommended requirements on the drug uses of various ingredients should not establish requirements or inferences for cosmetic uses of the ingredients. The comment cited menthol, methyl salicylate, and captan as ingredients that are regularly used in cosmetics, but which lack sufficient evidence of effectiveness to permit their classification as Category I ingredients for control of dandruff.

The comment urged the agency to include a statement that the OTC drug monograph will "cover only the drug use of the active ingredients listed therein" and that "the concentration range, limitations, warnings, and directions established for these ingredients in the monograph will not apply to the use of the same ingredients in products intended soley as cosmetics." The comment pointed out that a similar statement was included in the preamble to the tentative final monograph for OTC skin protectant drug products, published in the **Federal Register** of February 15, 1983 (48 FR 6820).

OTC drug rulemakings cover only the drug use of certain active ingredients. The concentration range, limitations, warnings, and directions established in an OTC drug monograph do not apply to the cosmetic use of ingredients, such as menthol, methyl salicylate, and captan when used in products labeled solely as cosmetics. However, if a product is intended for both drug and cosmetic use, it must conform to the requirements of the final OTC drug monograph.

The agency believes that the statement requested by the comment, i.e., that the monograph will "cover only the drug use of the active ingredients listed therein" is unnecessary because § 358.701(a) (Scope) and § 358.703 (Definitions) clearly limit the coverage of the monograph to drug products and do not apply to cosmetics. (See comment 3 above.)

In the preamble to the tentative final monograph for OTC skin protectant drug products, the agency proposed that the term "drug" be substituted for "agent" as a clarification of the scope and definition of a skin protectant (48 FR 6822 to 6823). Because the term "drug" has already been included in the scope and definition sections of the Panel's recommended monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products, no change is necessary in those sections of the present tentative final monograph.

B. Comments on Active Ingredients

5. Numerous comments objected to the Panel's Category III classification of coal tar preparations for use on the body. The comments noted that although the Panel was interested in long-term prospective studies in order to resolve theoretical concerns regarding the carcinogenic potential of coal tar products, it was clearly the Panel's intent for these preparations to remain available over-the-counter. Several comments also stated that data from 25-year retrospective studies on the safety of coal tar were presented to the Panel, but that the Panel did not adequately consider these data in its final report. The comments stated that the results of these studies, which have now been published (Refs. 1 and 2), provide reassurance that the clinical use of coal tar does not significantly alter the frequency of neoplasms.

Several comments cited additional publications that were not available to the Panel as further support for the safety of coal tar preparations (Refs. 3 through 6). One comment noted that although one recent study (Ref. 7) showed an increase in cancer rates in certain patients treated with coal tar, the study population was also receiving 8-methoxypsoralen photochemotherapy, which in itself may be a carcinogen or malignancy promoter.

One comment stated that the benefits of using coal tar in treating psoriasis far outweigh any theoretical risk or the risks associated with currently available alternative therapies. One comment suggested that any theoretical risks could be adequately handled by label warnings. The comment recommended labeling that would: (1) advise consumers to consult a physician every 6 months while using these products; and (2) advise consumers not to combine the use of products containing coal tar with other forms of therapy, such as ultraviolet radiation, unless directed by a physician.

Based on the available data and information, the agency concludes that coal tar preparations can be generally recognized as safe and effective for OTC use in controlling dandruff, seborrheic dermatitis, and psoriasis of the scalp or body.

As the Panel discussed in its report, it is well-established that coal tar contains substances that possess carcinogenic properties (47 FR 54657). Although there are reports in the literature regarding the development of neoplasms in patients who have had a history of coal tar use (Refs. 7 through 12), the reports are sporadic and are complicated by the fact that the patients were often exposed to multiple treatments, including ionizing radiation, arsenic, and ultraviolet radiation, as well as coal tar. The agency recognizes the difficulty in drawing definitive conclusions regarding coal tar from these studies.

Since the Panel completed its review of coal tar, two 25-year retrospective studies on coal tar use have been published in the literature (Refs. 1 and 2). One study included 260 patients with psoriasis who were hospitalized and treated with crude coal tar and ultraviolet radiation and who subsequently used coal tar preparations to control their psoriasis (Ref. 1). The other study included 305 patients with atopic dermatitis and neurodermatitis who were hospitalized and treated with coal tar and utltraviolet light (Ref. 2). The use of coal tar products after initial treatment varied in this study from none to daily use for 26 years. In both studies, groups were compared by examining multiple characteristics that may have affected eventual outcome. In neither study was the number of patients in whom skin cancer developed significantly different from the expected incidence for selected populations of the

United States. Others have reported similar results (Refs. 3 through 6).

Although none of these studies can be used to conclude definitively that the therapeutic use of coal tar is totally free of carcinogenic risk, they do provide adequate evidence that the risk, if it does exist, is relatively small. The agency also recognizes that the risks associated with coal tar use are less than the risks associated with alternative forms of psoriasis therapy.

The agency believes that the benefits to be derived from the use of coal tar outweigh the potential risks. Therefore, the agency is proposing that coal tar preparations be reclassified in Category I in this tentative final monograph. However, because the potential risks cannot be totally dismissed, the agency agrees with the one comment that the labeling of coal tar products should advise consumers not to use these products for prolonged periods of time without consulting a physician and not to use other forms of psoriasis therapy with coal tar unless directed by a doctor. Therefore, the following warnings are being proposed in the tentative final monograph: (1) "Do not use for prolonged periods without consulting a doctor." and (2) "Do not use this product with other forms of psoriasis therapy such as ultraviolet radiation or prescription drugs unless directed to do so by a doctor."

Although coal tar preparations are being proposed as Category I in this tentative final monograph, the agency advises that if new data become available demonstrating that use of coal tar preparations is associated with a significant risk of skin cancer, FDA will reexamine this classification in preparing the final monograph.

References

(1) Pittelkow, M.R., et al., "Skin Cancer in Patients With Psoriasis Treated With Coal Tar," *Archives of Dermatology*, 117:465–468, 1981.

(2) Marxgham, W.Z., et al., "Incidence of Skin Cancers In Patients With Atopic Dermatitis Treated With Coal Tar," *Journal of the American Academy of Dermatology*, 3:612–615, 1980.

(3) Menter, A., and D.L. Cram, "The Goeckerman Regimen in Two Psoriasis Day Care Centers," *Journal of the American Academy of Dermatology*, 9:59–65, 1983.

(4) Anderson, T.F., "Psoriasis," *Medical Clinic of North America*, 66:769–799, 1982.

(5) Gotz, H., B. Deichmann, and M. Zabel, "Regarding the Question of Iatrogenic Carcinoma Prevention through the Use of Tar in Dermatology," *Zietschrift fur Hautkrankheiten*, 55:751–755, 1978.

(6) Larko, O., and G. Swanbeck, "Is UVB Treatment of Psoriasis Safe? A Study of Extensively UVB-Treated Psoriasis Patients Compared with a Matched Control Group," *Acta Dermatologica-Venereologica*, 62:507–512, 1982.

(7) Stern, R.S., S. Zierler, and J.A. Parrish, "Skin Carcinoma In Patients With Psoriasis Treated With Topical Tar and Artificial Ultraviolet Radiation," *Lancet*, 1:732–735, 1980.

(8) Rook, A.J., et al., "Squamous Epithelioma Possibly Induced By Therapeutic Application of Tar," *British Journal of Cancer*, 10:17–23, 1956.

(9) Greither, A., C. Gisbertz, and H. Ippen, "Teerbehandlung und Kreba," *Zeitschrift fur Hautkrankheiten*, 42:631–635, 1967.

(10) Lagerholm, B., and E. Skog, "Squamous Cell Carcinoma In Psoriasis Vulgaris: Three Cases of Squamous Cell Carcinoma Developing in Psoriatic Lesions," *Acta Dermato Venereologica*, 48:128–136, 1968.

(11) Denkin, W., et al., "Melanoma In a Patient Treated For Psoriasis," *Southern Medical Journal*, 71:732–733, 1978.

(12) Kaaber, K., "Occurrence of Malignant Neoplasma in Patients With Atopic Dermatitis," *Acta Dermato Venereologica*, 56:445–447, 1976.

6. Two comments questioned the dosage range for coal tar solution in shampoos, One comment pointed out that coal tar solution is at most 20 percent coal tar USP, and that the Panel's recommended lower dosage limits of coal tar USP (0.5 percent) and coal tar solution (2.5 percent) reflect this relationship, but that this 5 to 1 ratio is not reflected in the upper dosage limit of 5 percent recommended by the Panel for both preparations. The comment suggested that the upper dosage limits be adjusted to reflect this relationship and recommended that 15 percent coal tar solution and 3 percent coal tar USP be used. The second comment stated that, at its 37th meeting, the Panel discussed and approved a number of marketed concentrations of coal tar solution shampoos including a 7.5 percent dosage, but that the advance notice of proposed rulemaking contains an upper limit of 5 percent coal tar solution. The comment asserted that the Panel intended to include the 7.5 percent coal tar solution in its recommendation for Category I dosages and requested that this dosage be included in the proposed rule.

The agency believes that the Panel based its concentration ranges for coal tar preparations on data submitted for marketed products and not on any particular relationship between coal tar and coal tar solution. Although the comment is correct that coal tar solution USP is at most 20 percent coal tar USP, the agency does not believe that the concentration ranges for coal tar and coal tar solutions should be based solely on this relationship. In determining the appropriate concentration limits for coal tar preparations, the agency has considered the comments filed by the Joint Industry Coal Tar Committee (JICTC) (Ref. 1) and is proposing in comment 7 below to redefine the concentration ranges of coal tar preparations in terms of the relative coal tar content. These proposed revisions will also provide for the higher concentration coal tar solution product requested by the one comment.

Reference

(1) Report of the Joint Industry Coal Tar Committee, Comment C00021, Docket No. 82N–0214, Dockets Management Branch.

7. One comment objected to the Panel's discussion of the chemistry of coal tar at 47 FR 54656. The comment stated that, while some recent references were cited, statements relating to descriptions of coal tar fractionization rely on old references even through more recent information was available to the Panel. The comment stated that the submission by The Proprietary Association (Ref. 1) that was presented to the Panel at its last meeting provided a more appropriate description of coal tar, but that this submission was not addressed by the Panel. Another comment also endorsed The Proprietary Association submission stating that submission included a proper definition of coal tar USP and its solutions, fractions, and extracts. The comment also provided information comparing its special coal tar extract to coal tar topical solution, USP, and contended that the two extracts have similar properties in spite of manufacturing differences.

A third comment submitted the interim report of the JICTC (Ref. 2) describing the industry's efforts in developing more definitive specifications for medicinal coal tar as opposed to tars used for other purposes. The comment suggested that medicinal coal tar be defined as the tar obtained as a byproduct during the destructive distillation bituminous coal at temperatures in the range of 900° C to 1100° C. The comment stated that specifying the carbonization temperature would insure a more uniform coal tar because the composition of the tar is dependent on the carbonization temperature used. The comment also noted the JICTC's intention to present its recommendations regarding coal tar standards to the USP as soon as its work is completed.

After reviewing the available data, the agency acknowledges that, due to the complex chemistry of coal tar and its extracts and distillates, specifications additional to those recommended by the Panel and those contained in the USP

XXI may be necessary for describing these products in the monograph.

Based on the JICTC report (Ref. 2), the agency believes that for proposes of the OTC drug monograph, coal tar should be defined as "the tar used for medicinal purposes that is obtained as a byproduct during the destructive distillation of bituminous coal at temperatures in the range of 900 °C to 1100 °C. It may be further processed using either extraction with alcohol and suitable dispersing agents and maceration times or fractional distillation with or without the use of suitable organic solvents. The concentration of the coal tar portion of the final product should be in a relative concentration range of 0.5 to 5 percent coal tar." The agency believes that this definition reflects the coal tar that is currently being used for medicinal purposes and will provide for sufficient flexibility in the marketing of coal tar products because coal tar solutions and coal tar extracts in final formulation are essentially similar in that they contain the same relative concentration of coal tar and exhibit little difference in therapeutic activity. The agency invites specific comments on these proposed coal tar specifications. The agency commends the industry's efforts in developing more definitive specifications and urges their continued involvement and cooperation in assuring adoption of more definitive specifications for inclusion in the USP.

References

(1) Unpublished data, Comment C00020, Docket No. 82N–0214, Dockets Management Branch.

(2) Report of the Joint Industry Coal Tar Committee, Comment C00021, Docket No. 82N–0214, Dockets Management Branch.

8. One comment contended that 1 percent selenium sulfide is safe and effective for the treatment of seborrheic dermatitis of the scalp as well as for dandruff. The comment submitted a study in which 1 percent selenium sulfide shampoo was used by 10 patients with seborrheic dermatitis (Ref. 1). The comment stated that the National Academy of Sciences/National Research Council (NAS/NRC) Drug Efficacy Study Group and FDA recognized a 2.5-percent concentration of selenium sulfide as safe and effective for seborrheic dermatitis. (See the **Federal Register** of July 17, 1971; 36 FR 13286.) The comment also noted that the Panel clearly stated in its report that "ingredients effective in relieving the symptoms of dandruff will also relieve the symptoms of seborrheic dermatitis" (47 FR 54655).

The Panel placed a 1-percent concentration of selenium sulfide in Category III for the OTC treatment of seborrheic dermatitis of the scalp because it was not aware of data to demonstrate that the 1 percent concentration effectively controls seborrheic dermatitis. However, the study by Jean et al. (Ref. 1) submitted by the comment demonstrates clinically significant improvement in 9 out of 10 patients with medium-severe to severe seborrheic dermatitis during the course of a 30-day treatment period. This study, designed as a safety study, demonstrated no adverse effects and no statistically significant increase in plasma and urinary levels of selenium and also demonstrated the effectiveness of 1 percent selenium sulfide in controlling seborrheic dermatitis.

In view of the results of this study the agency is proposing Category I status for 1 percent selenium sulfide for seborrheic dermatitis.

Reference

(1) Jean, Y., et al., "Plasma Levels and Urinary Excretion of Selenium After Application of a 1% Selenium Sulfide Shampoo to Patients with Seborrheic Dermatitis," Selenium in Biology and Medicine, "Proceeding of the International Symposium 2nd, 1980," pp. 422–426, 1981.

9. One comment stated that the Panel, in making its recommendations on the safety and effectiveness of a 2- to 5-percent sulfur preparation for the treatment of dandruff, based its conclusions on the interim report of an 8-week study (Ref. 1). The comment submitted the final report on that 8-week study (Ref. 2) and pointed out that the results confirm that a 2- to 5-percent concentration of sulfur in a shampoo dosage form is superior to shampoo alone in the treatment of dandruff. The comment added that the final report contained the additional finding that 5 percent sulfur shampoo was statistically superior to 2 percent sulfur shampoo in the treatment of dandruff. The comment also asserted that the Panel in its discussion of the interim report on this study erroneously stated that corneocyte counts were made, when in fact, no corneocyte counts were performed in this study.

The agency acknowledges the erroneous mention of corneocyte counts in connection with the interim report on this study. The Panel concluded that sulfur is safe and effective in concentrations of 2 to 5 percent for OTC topical use for controlling dandruff. The final report (Ref. 2) further confirms the Panel's conclusions.

References

(1) Meltzer, N., Presentation at 42d Meeting of the Advisory Review Panel on Miscellaneous External Drug Products, November 7, 1980.

(2) Rapaport, M., unpublished study IRSI208HCO880, Comment C0019, Docket No. 82N–0214, Dockets Management Branch.

10. Two comments asserted that the concentration ranges for pyrithione zinc recommended by the Panel in § 358.710 (e) and (f) must be related to specific product forms because as currently stated any of the concentrations could be used in a hairgroom or in a shampoo. The comments stated that it was clearly the Panel's intention that ". . . preparations containing 1 to 2 percent zinc pyrithione in a shampoo and 0.1 to 0.25 percent zinc pyrithione in a hairgroom are effective in controlling dandruff and seborrheic dermatitis" (47 FR 54666).

The comments requested that the concentration ranges for pyrithione zinc be clearly designated as specific product forms to avoid confusion.

The agency agrees that clarification of the monograph is necessary. The tentative final monograph designates the higher concentration range of pyrithione zinc for product formulations that are intended to be applied and then washed off after brief exposure and the lower concentration range for product formulations that are intended to remain on the skin or scalp.

11. One comment requested that the lower limit of the concentration range for pyrithione zinc in dandruff shampoos be changed from 1 percent to 0.95 percent. The comment pointed out that this slight adjustment in the minimum concentration would permit manufacturers to produce a single formulation for both United States and international markets. The comment explained that some countries, e.g., Germany, permit the sale of pyrithione zinc only at dosage levels of "less than one percent." To support its request, the comment submitted a 35-day clinical study of the effectiveness of a shampoo containing 0.95 percent pyrithione zinc (Ref. 1).

The data submitted by the comment show that the 0.95-percent pyrithione zinc shampoo formulation produced significant improvement in the patients' conditions as measured by degree of scaling and by corneocyte counts. In addition, the agency notes that the requested change in concentration is very slight, is not apt to cause any decrease in product effectiveness, and will allow for manufacturers to market a single product that could be sold both in the United States and in foreign markets. Therefore, the agency is proposing in this tentative final monograph that the lower limit of

pyrithione zinc be changed from 1.0 percent to 0.95 percent.

Reference

(1) Unpublished study, Comment C0017, Docket No. 82N–0214, Docket Management Branch.

12. One comment questioned the validity of the Panel's conclusions that borate preparations are not safe for the treatment of dandruff and seborrheic dermatitis. The comment noted that products reviewed by the Panel contained only 0.5 percent boric acid or 0.47 percent sodium borate and expressed the opinion that the Panel based its conclusions on predetermined opinion without objectively evaluating literature findings or considering the concentrations of boric acid and sodium borate used in dandruff preparations.

The comment stated that the LD_{50} in rats is over 3,100 milligrams per kilogram (mg/kg) for either boric acid or sodium borate. The comment called attention to a 2-year feeding study on rats and dogs by Weir and Fisher that apparently was not considered by the Panel (Ref. 1). The comment requested the agency to reevaluate the Panel's conclusions on the safety of boric acid and sodium borate.

The agency has reviewed all available data on borates including the reports of other OTC panels. The Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products, after studying the problem of borate absorption through vaginal tissue, concluded in both its report on OTC vaginal contraceptive drug products, published in the **Federal Register** of December 12, 1980 (45 FR 82014), and its report on OTC vaginal drug products, published in the **Federal Register** of October 13, 1983 (48 FR 46694), that boron compounds were safe for use in the vaginal area in concentrations of up to 1 percent as preservatives. (See 45 FR 82042 and 48 FR 46712.) The Advisory Review Panel on OTC Ophthalmic Drug Products concluded in this report, published in the **Federal Register** of May 6, 1980 (45 FR 30002), that borates were safe for use in infected eyes at up to 5 percent concentrations. (See 45 FR 30029.) The Advisory Review Panel on OTC Antimicrobial II Drug Products concluded in its report on OTC topical antifungal drug products, published in the **Federal Register** of March 23, 1982 (47 FR 12480), and in its report on OTC topical acne drug products, which was published the same day (47 FR 12430), that borates were safe for topical application at up to 5 percent concentrations. (See 47 FR 12528 and 47 FR 12452.)

Based on the above Panel reports as well as its own review of the data, the agency concludes that there is ample evidence to support the safety of up to 1 percent concentration of borates for OTC use in dandruff and seborrheic dermatitis preparations. Although the agency believes that the safety of borates in concentrations used in OTC dandruff and seborrheic dermatitis drug products (up to 1 percent) has been adequately demonstrated, the effectiveness of these compounds for the treatment of those conditions has not been demonstrated. Therefore, the agency concludes, that in concentrations of 1 percent or less, boric acid and sodium borate are considered Category II for effectiveness.

Reference

(1) Weir, R.J., and R.S. Fisher, "Toxicologic Studies on Borax and Boric Acid," *Toxicology and Applied Pharmacology*, 23:351–364, 1972.

13. One comment requested that 0.25 to 1 percent hydrocortisone be reclassified as Category I for the treatment of seborrheic dermatitis. The comment asserted that data submitted to the Panel (Ref. 1) establish the safety and effectiveness of these concentrations of hydrocortisone in the treatment of seborrheic dermatitis.

The data referred to by the comment were initially submitted to the Miscellaneous External Panel, but were not reviewed by the Panel during the development of its report on OTC dandruff, seborrheic dermatitis, and psoriasis drug products. Subsequently, the agency has reviewed the data and concludes that these data, together with the conclusions of the NAS/NRC, Drug Efficacy Study Group, which were published in the **Federal Register** of April 28, 1971 (36 FR 7982), support the general recognition of the safety and effectiveness of hydrocortisone in providing temporary symptomatic relief of the inflammation and itching associated with seborrheic dermatitis and psoriasis.

Hydrocortisone has been shown to be beneficial in treating the redness and itching associated with a wide variety of dermatoses, and is classified as a Category I ingredient in the tentative final monograph for OTC external analgesic drug products that was published in the **Federal Register** of February 8, 1983 (48 FR 5852). In that tentative final monograph, the agency proposed that 0.25 to 0.5 percent hydrocortisone be generally recognized as safe and effective for OTC use in relieving the symptoms associated with a variety of dermatoses. Because the symptoms included in that rulemaking, i.e., itching, irritation, and inflammation, are very similar to those associated with seborrheic dermatitis and psoriasis, the agency believes that it would be more approporiate to amend the tentative final monograph for OTC external analgesic drug products to add seborrheic dermatitis and psoriasis to the list of conditions for which hydrocortisone has been found to be safe and effective in providing symptomatic relief rather than to include hydrocortisone as an ingredient in the tentative final monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products. In this way, the various conditions for which hydrocortisone is considered generally recognized as safe and effective for OTC use will be listed in one monograph.

Therefore, elsewhere in this issue of the **Federal Register**, the agency is proposing to amend the proposed rule for OTC external analgesic drug products to include seborrheic dermatitis and psoriasis as conditions for which hydrocortisone and hydrocortisone acetate have been found to be safe and effective in providing symptomatic relief. The agency notes that the dosage range for hydrocortisone requested by the comment exceeds that proposed for hydrocortisone in the tentative final monograph for OTC external analgesic drug products. The agency will consider the request that concentrations of hydrocortisone greater than 0.5 up to 1 percent be classified as Category I in developing a final monograph for OTC external analgesic drug products.

Reference

(1) OTC Volumes 160061 to 160066, Docket No. 82N–0214, Dockets Management Branch.

14. One comment requested that the agency classify chloroxylenol in Category I for safety. The comment asserted that although the Miscellaneous External Panel concluded that there was a lack of subchronic data, the Advisory Review Panel on Antimicrobial II Drug Products, in its report on OTC topical antifungal drug products (47 FR 12535), considered such data and concluded that chloroxylenol is safe for OTC use as a topical antifungal in concentrations of up to 3.75 percent.

Although the Antimicrobial II Panel concluded that chloroxylenol was safe for short-term use (up to 13 weeks), it expressed concern over the effects that chronic administration of this drug may have on the liver (47 FR 12534). At this time, the agency is evaluating all available data on the safety of chloroxylenol under the rulemaking for

OTC topical antimicrobial drug products (Docket No. 75N–0183). The conclusions reached by the agency on the safety of topical chloroxylenol under that rulemaking will also apply to this rulemaking. Until the evaluation is completed, chloroxylenol will remain in Category III in this rulemaking for safety.

15. On comment requested that undecylenic acid moneothanolamide sulfosuccinate sodium salt be reclassified as Category I for safety in the treatment of dandruff and seborrheic dermatitis. The comment argued that because only one of the six toxicologic studies submitted on this compound was cited by the Panel, these safety data do not appear to have been fully considered (Refs. 1 through 6). The comment suggested that this may have been due to confusion resulting from the use of different trade names and trademarks to identify this same ingredient in different studies.

The comment further suggested that the Panel may have placed undue emphasis on this compound being an undecylenate preparation when it might well be described both chemically and functionally as a sulfosuccinate, a class of compounds widely used in skin contact products in the cosmetic industry. The comment pointed out that there was no evidence of treatment-related primary irritation or secondary sensitization in the efficacy studies submitted on this compound (Refs. 7 and 8).

The comment added that this compound has been used in antidandruff shampoos in Europe and Canada for over 20 years and has been used in cosmetic shampoos in the United States with no reports of skin or eye irritation or any toxic reaction.

The agency has reviewed the six toxicologic studies cited by the comment. These studies include the following: (1) A 7-day rabbit eye irritation study in which no signs of irritation were shown using a 5-percent solution of this compound (Ref. 1); (2) a test of various concentrations of the compound from 0.39 to 50 percent for anesthetic effects on rabbit eyes; the results showed no anethesia was produced and that significant irritation occurred only at the 50 percent concentration (Ref. 2); (3) a guinea pig skin sensitization test by the Draize method which demonstrated that this compound is not a sensitizer (Ref. 3); (4) an acute oral toxicity test in rats which showed an LD_{50} greater than 10 grams per kilogram (g/kg) (Ref. 4); (5) an acute toxicity test by subcutaneous injection in mice which showed an LD_{50} greater than 2 g/kg (Ref. 6); (6) a subacute dermal toxicity test in rabbits which showed mild to moderate skin irritation but no toxicity from application of up to 1.428 milliliters per kilogram (ml/kg) of a 50-percent concentration of undecylenic acid monoethanolamide sulfosuccinate sodium salt daily for 20 days (Ref. 5). In addition, a high dose (50-percent concentration) eye irritation study in nine rabbits produced only one corneal lesion that had not healed within 7 days. No iris lesions were produced (Ref. 9). In view of the above toxicity data and the long history of use of this compound in shampoo type products in this and other countries, the agency concludes that undecylenic acid monoethanolamide sulfosuccinate sodium salt is safe for topical use up to the 2-percent level recommended by the Panel.

The agency notes, however, that this compound, although it has been used in cosmetic shampoos, has never been marketed in this country for the treatment of dandruff, psoriasis, or seborrheic dermatitis, whereas another undecylenate salt, calcium undecylenate, has been marketed for the treatment of these conditions. Although effectiveness testing of this compound is currently underway (Ref. 10), this compound was classified as Category III by the Panel for the treatment of dandruff, psoriasis, or seborrheic dermatitis. Under agency policy, it may not be marketed in OTC drug products for these indications until it has Category I status in an OTC drug monograph or is the subject of an approved application.

Reference

(1) "Acute Eye Irritation Test with 5% Loramine SBU–185," Consultox Laboratories Ltd., London, unpublished study, Comment C0018, Docket Number 82N–0214, Dockets Management Branch.

(2) "Anesthetic Effect on the Eye of SBU–185," Kolmar Research Center, Weisbaden-Igstadt, unpublished study, Comment C0018, Docket Number 82N–0214, Dockets Management Branch.

(3) "Skin Sensitization Testing of SBU–185," Kolmar Research Center, Weisbaden-Igstadt, unpublished study, Comment C0018, Docket Number 82N–0214, Dockets Management Branch.

(4) "Acute Oral Toxicity Testing in Rats of SBU–185," Kolmar Research Center, Weisbaden-Igstadt, unpublished study, Comment C0018, Docket Number 82N–0214, Dockets Management Branch.

(5) "Sub Acute Dermal Toxicity Testing in Rabbits with SBU–185," Kolmar Research Center, Weisbaden-Igstadt, unpublished study, Comment C0018, Docket Number 82N–0214, Dockets Management Branch.

(6) "Acute Toxicity Test in Mice of SBU–185," Institute for Industrielle und Biologische Forschung, Steinau, unpublished study, Comment C0018, Docket Number 82N–0214, Dockets Management Branch.

(7) Lubowe, I.I., "The Treatment of Seborrhea Capitis with Undecylenic Alkanolamides," *Soap, Perfumery, and Cosmetics*, 35:908, 1962.

(8) Alexander, S., "Do Shampoos Affect Dandruff?," *The British Journal of Dermatology*, 79:92–95, 1967.

(9) "Primary Irritation of Mucus Membranes with 50% SBU–185," Kolmar Research Center, Weisbaden-Igstadt, unpublished study, Comment C0018, Docket Number 82N–0214, Dockets Management Branch.

(10) Letter from W.E. Gilbertson, FDA, to Sherex Chemical Company, Inc., April 12, 1984, Comment LET003, Docket Number 82N–0214, Dockets Management Branch.

C. Comments on Labeling

16. Several comments argued that FDA cannot legally and should not, as a matter of policy, prescribe exclusive lists of terms from which indications for use of OTC drug products must be drawn, thus prohibiting alternative OTC labeling terminology that is truthful, not misleading, and intelligible to the consumer. One comment argued that such a policy is an unconstitutional restriction of commercial speech and exceeds FDA's statutory authority. Another comment argued that labeling requirements for OTC drug products can create no inferences for cosmetics, or for the cosmetic aspects of the labeling of those products that are marketed as cosmetics as well as drugs, for example, a cosmetic dandruff shampoo (a product represented both to treat dandruff and to leave the hair clean and manageable). The comment asserted that FDA accepted this principle in the tentative final monograph for OTC skin bleaching drug products, which was published in the **Federal Register** of September 3, 1982 (47 FR 39115), where it stated that "The agency emphasizes that OTC drug monographs contain appropriate drug labeling claims to be used on OTC drug products and do not preclude the use of acceptable cosmetic claims if the product is both a drug and a cosmetic."

Two comments submitted extensive lists proposing that the following terminology and "other truthful statements" be added as acceptable indications: "fights itching and scalp flaking . . .," "reduces itching, irritation, and skin flaking . . .," "controls itching, redness, and scaling . . .," "helps eliminate . . .," "helps stop . . .," "controls recurrence of . . .," "reduces recurrence of . . .," "helps prevent . . .," and "fights recurrence of . . ." dandruff, seborrheic dermatitis, and/or psoriasis.

During the course of the OTC drug review, the agency has maintained that the terms that may be used in an OTC

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

During the course of the review, FDA's position on the "exclusivity policy" has been questioned many times in comments and objections filed in response to particular proceedings and in correspondence with the agency. The agency has also been asked by The Proprietary Association to reconsider its position. In a notice published in the **Federal Register** of July 2, 1982 (47 FR 29002), FDA announced that a hearing would be held to assist the agency in resolving this issue. On September 29, 1982, FDA conducted an open public forum at which interested parties presented their views. The forum was a legislative type administrative hearing under 21 CFR Part 15 that was held in response to a request for a hearing on the tentative final monographs for nighttime sleep-aids and stimulants (published in the **Federal Register** of June 13, 1978; 43 FR 25544).

After considering the testimony presented at the hearing and the written comments submitted to the record, in the **Federal Register** of April 22, 1985 (50 FR 15810), FDA proposed to change its exclusivity policy for the labeling of OTC drug products. In the **Federal Register** of May 1, 1986 (51 FR 16258), the agency published a final rule changing the exclusivity policy and establishing three alternatives for stating the indications for use in OTC drug labeling. Under the final rule, the label and labeling of OTC drug products are required to contain in a prominent and conspicuous location, either (1) the specific wording on indications for use established under an OTC drug monograph, which may appear within a boxed area designated "APPROVED USES"; (2) other wording describing such indications for use that meets the statutory prohibitions against false or misleading labeling, which shall neither appear within a boxed area nor be designated "APPROVED USES"; or (3) the approved monograph language on indications, which may appear within a boxed area designated "APPROVED USES," plus alternative language describing indications for use that is not false or misleading, which shall appear elsewhere in the labeling. All required OTC drug labeling other than indications for use (e.g., statement of identity, warnings, and directions) must appear in the specific wording established under an OTC drug monograph.

After reviewing the Panel's recommendations as well as the extensive list of indications submitted with the comments, the agency is proposing the following indication for inclusion in the monograph:

(1) ("For relief of" or "Controls") "the symptoms of" (select one or more of the following, as appropriate: "dandruff," "seborrheic dermatitis," and/or "psoriasis.")

(2) The following terms may be used in place of the words "the symptoms of" in the indications in paragraph (1) of this section: ("skin" and/or "scalp," as appropriate) (select one or more of the following: "itching," "irritation," "redness," "flaking," "scaling,") "associated with").

For example, an allowable indication would read as follows: "For the relief of scalp itching and flaking associated with dandruff."

The agency believes that these statements accurately reflect the indications for use of OTC dandruff, seborrheic dermatitis, and psoriasis drug products and provide for the necessary flexibility in developing appropriate indications for the wide range of product formulations. Other terms suggested by the comments are examples of truthful and nonmisleading language that may be used elsewhere in the labeling. In this tentative final monograph, supplemental language relating to indications has been proposed and captioned as *Other Allowable Statements*. Under FDA's revised exclusivity policy (51 FR 16258), such statements are included at the tentative final stage as examples of other truthful and nonmisleading language that would be allowed elsewhere in the labeling without prior FDA review. In accordance with the revised exclusivity policy, such statements would not be included in a final monograph. However, the agency has decided that, because these additional terms have been reviewed by FDA, they should be incorporated, wherever possible, in final OTC drug monographs under the heading "Indications" as part of the indications developed under the monograph.

The agency agrees with the comment that the labeling restrictions in this tentative final monograph apply only to products that fall within the statutory definition of "drugs" and not to cosmetic products. This distinction between drugs and cosmetics is discussed in comment 3 above.

The final monograph will cover only the drug use of the active ingredients listed therein. The concentration range, limitations, statements of identity, indications, warnings, and directions established for these ingredients in the monograph will not apply to the use of the same ingredients in products intended solely as cosmetics. However, if a product is intended for both drug and cosmetic use, it must conform to the requirements of the final monograph. In addition to the indications allowed for OTC dandruff, psoriasis, and seborrheic dermatitis drug products, such products may also bear appropriate labeling for cosmetic uses, in conformity with section 602 of the act (21 U.S.C. 362) and the provisions of 21 CFR Part 701. In accordance with the final rule on the agency's "exclusivity policy" (51 FR 16258), it is the agency's view that cosmetic claims may not appear within the boxed area designated "APPROVED USES." As discussed at 51 FR 16264 (paragraph 14), cosmetic claims may appear elsewhere in the labeling but not in the box should manufacturers choose the labeling alternative provided in § 330.1(c)(2) (i) or (iii) for labeling consmetic/drug products.

17. Two comments argued that statements which accurately and effectively identify the product to the nontechnical consumer should be acceptable as a statement of identity. Both comments suggested "antidandruff (product form, such as shampoo)" and "dandruff (product form)" as alternative statements of identity that are truthful, not misleading, and meaningful to laymen.

The agency agrees that the statements of identity suggested by the comments are valid examples of truthful and nonmisleading labeling. The agency concludes that these statements of identity are clearer than those originally recommended by the Panel and has incorporated them in this tentative final monograph as replacements for the statements of identity recommended by the Panel. The agency has also revised

the statements of identity for seborrheic dermatitis, psoriasis, and cradle cap drug products to read as follows: "seborrheic dermatitis (insert product form)," "psoriasis (insert product form)" and "cradle cap (insert product form)".

18. One comment requested that provisions be made to allow any product with more than one applicable indication to combine those indications to eliminate duplicate words because of limited labeling area. The comment noted that the Panel took this approach in § 358.750(a)(6) for the statement of identity declaration. The comment requested that the following new paragraph be added to recommended § 358.750(b): "The statements of indications for any product with more than one indication identified in paragraph (b) of this section may be combined to eliminate duplicate words."

In developing this tentative final monograph, the agency has revised the indications statements in a manner that will avoid duplication. (See comment 16 above.) Because the indications allow sufficient flexibility, the paragraph suggested by the comment is unnecessary.

19. One comment indicated agreement with the Panel's statement in its discussion of labeling that it is "unacceptable to use any claims related to product performance unless they can be substantiated by adequate scientific data" (47 FR 54655). However, the comment expressed concern that the Panel's comments appear to suggest that the "adequate scientific data" to support the validity of such claims as "fast" or "long acting" should be presented directly to the consumer in product labeling.

While the Panel expressed its convictions that claims related to product performance are "unacceptable" unless supported by scientific data, there was no intention on the part of the Panel to require that such data be routinely forwarded to the public as part of the labeling.

The OTC drug review program establishes conditions under which OTC drugs are generally recognized as safe and effective and not misbranded. Two principal conditions examined during the review are allowable ingredients and allowable labeling. The FDA has determined that it is not practical—in terms of time, resources, and other considerations—to set standards for all labeling found in drug products. Accordingly, OTC drug monographs regulate only labeling related in a significant way to the safe and effective use of covered products by lay persons. OTC drug monographs establish allowable labeling for the following items: product statement of identity; names of active ingredients; indications for use; directions for use; warnings against unsafe use, side effects, and adverse reactions; and claims concerning mechanism of drug action.

As with all OTC drug products, dandruff, psoriasis, and seborrheic dermatitis products are expected to achieve their intended results within a reasonable period of time. However, the specific period of time within which these products achieve these results is not related in a significant way to the safe and effective use of the products. Therefore, terms such as "fast" or "long acting" are outside the scope of the OTC drug review.

Such statements or terms will be evaluated by the agency on a product-by-product basis, under the provision of section 502 of the act (21 U.S.C. 352) relating to labeling that is false or misleading. Moreover, any term that is outside the scope of the review, even though it is truthful and not misleading, may not appear in any portion of the labeling required by the monograph and may not detract from such required information. However, terms outside the scope of the monograph may be included elsewhere in the labeling, provided they are not false or misleading.

20. A number of comments stated that the directions recommended by the Panel in its monograph were too narrow, unnecessarily restrictive, and neither applicable nor adequate for all types of products and dosage forms covered by this monograph. Several comments stated that the Panel had intended to include dosage forms other than shampoos and hairgrooms in the monograph because at 47 FR 54654 the Panel recognized that dandruff, seborrheic dermatitis, and psoriasis preparations were marketed in other forms. The comments urged that these other dosage forms be provided for in the monograph. Two comments specifically urged simpler and more general directions and asked that firms be allowed to include additional directions for use suitable to their specific product form. A number of comments urged that the directions include provisions for preshampoo and postshampoo rinse dandruff formulations as well as bar soap formulations of coal tar.

Other comments objected to the Panel's limitations of "twice-a-week" usage for antidandruff shampoos. The comments stated that if consumers are limited to twice-a-week use of antidandruff shampoos, it is probable that they will use a cosmetic shampoo in between uses of the antidandruff shampoo because data indicate that people shampoo more frequently than twice a week. Thus, if a consumer used a cosmetic shampoo in conjunction with the twice-a-week usage of a medicated shampoo, especially with one where effectiveness depends on deposition and retention of the active ingredient, the consumer may be removing the active ingredient and, therefore, not achieving the clinically demonstrated benefit. The comments recommended that the directions for antidandruff shampoo products be revised to either "For best results, use regularly," or "For best results, use at least twice a week."

The agency agrees that the directions recommended by the Panel were too narrow and would not be applicable or adequate for all types of products covered by the monograph. Although there are a wide variety of formulations and dosage forms of OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis, all formulations and dosage forms fall into one of three basic groups: products formulated to be applied and then washed off after a brief (a few minutes) exposure (e.g., shampoos, preshampoo rinses, postshampoo rinses); products formulated to be applied up to four times daily and left on the skin or scalp (e.g., creams, ointments, lotions, hairgrooms); and products formulated as soaps, to be used in place of regular soaps, for the treatment of seborrheic dermatitis and psoriasis of the skin. Therefore, to accommodate the various dosage forms of dandruff, seborrheic dermatitis, and psoriasis drug products, the agency is including in the tentative final monograph only brief, required directions for each of the three basic groups of product formulations mentioned above. Manufacturers can then voluntarily expand and supplement these required directions with more detailed instructions applicable to a particular product formulation and dosage form.

The directions proposed in this tentative final monograph are as follows:

(1) *For products containing active ingredients for the control of dandruff, seborrheic dermatitis, or psoriasis when formulated to be applied and then washed off after brief (a few minutes) exposure (e.g., shampoos, preshampoo rinses, postshampoo rinses).* "For best results use at least twice a week or as directed by a doctor."

(2) *For products containing active ingredients for the control of dandruff, seborrheic dermatitis, or psoriasis when formulated so as to be applied and left on the skin or scalp (e.g., creams,*

ointments, lotions, hairgrooms). "Apply to affected areas one to four times daily or as directed by a doctor."

(3) *For products containing active ingredients for the control of seborrheic dermatitis or psoriasis of the skin when formulated as soaps.* "Use on affected areas in place of your regular soap."

21. Several comments requested that the warning in § 358.750(c)(1)(iii) be deleted from the Panel's recommended monograph. The warning states, "If condition worsens or does not improve after regular use of this product as directed, consult a doctor."

The comments contended that the warning is inappropriate and unwarranted for dandruff control drug products. To support this contention, they cited the Panel's statement that "if dandruff is left untreated, the resulting problems are problems of appearance; no medical disability will result" (47 FR 54652). The comments further argued that this warning is unnecessarily alarming and tends to dilute the value of the other warnings on dandruff control drug products. One of the comments also called attention to the Panel's statement that misdiagnosing seborrheic dermatitis of the scalp as dandruff is not of great consequence because the treatment for both is generally the same, nor is harm likely to follow if the consumer treats psoriasis with an antidandruff product (47 FR 54655). The comment pointed out that the warning in question was intended to apply to conditions that affect the body and do not respond to treatment or that affect a large area of the body.

Another comment argued that this warning should be deleted for psoriasis and seborrheic dermatitis as well as for dandruff control drug products.

The agency agrees that there is no major medical risk in leaving dandruff untreated or in misdiagnosing and treating seborrheic dermatitis or psoriasis as dandruff for a short period. However, the warning in question was intended to ensure that more serious dermatologic conditions that do not respond to treatment with OTC drug products, either because of the severity of the condition or because of misdiagnosis, are treated by a doctor.

The warning also serves to alert individuals who may be particularly sensitive or allergic to the product to discontinue use. Therefore, the warning is being included in the tentative final monograph.

22. Several comments urged deletion of the Panel's recommended warning in § 358.750(c)(1)(iv), "Do not use on children under two years of age except as directed by a doctor," as unwarranted and unnecessary for dandruff control drug products.

One comment cited the Panel's statement that because the usual onset of dandruff is in puberty, children under 2 years of age are unlikely to have dandruff (47 FR 54651). Several comments cited the long history of safe marketing and the already adequate margin of safety of dandruff control drug products. Even if the warning were needed for shampoo-type dandruff control drug products, one comment added, it would be unnecessary for medicated hairgroom products because the product vehicle and labeling are directed for use by adolescents and adults.

Another argument was that the warning dilutes the impact of more meaningful warnings and suggests to the consumer that dandruff control drug products are inherently unsafe and would produce unwanted reactions if used on young children. One comment suggested that if the warning is retained it be reworded to read "Use on children under 2 years of age only as directed by a (health professional, or physician or doctor)."

The agency agrees with the comments that the margin of safety of dandruff control drug products is sufficiently great that the occasional exposure of young children to these products should not constitute any major medical problem. In addition, the likelihood of children being exposed to the product is extremely small because children 2 years of age or less are not normally subject to dandruff and consequently do not customarily use these products. The warning against use by children under 2 years of age is therefore unnecessary and it is not being included in the tentative final monograph.

23. One comment subjected to the Panel's recommended warning is § 358.750(c)(1)(ii) "Avoid contact with the eyes, if this happens, rinse thoroughly with water" as unnecessary for antidandruff hair groom ointments intended for application to the scalp. The comment argued that this warning is unnecessary for antidandruff hair groom ointments because the essentially solid form of such products will not run into the eyes and cannot be accidently splashed or poured into the eyes. The comment stated that this request for deletion of the warning is consistent with the agency's position taken in regard to lip balm products at 48 FR 6829. (See the tentative final monograph for OTC skin protectant drug products published in the **Federal Register** of February 15, 1983; 48 FR 6820.)

The agency agrees that there is less risk of eye contact with the ointment dosage form than with shampoos. However, because the ointment must be applied and rubbed by hand there is the likelihood that the product can be transferred to the eye if the eyes are touched or rubbed or if contact lenses are touched before the hands are cleaned. The warning in question is based primarily on the eye irritation potential of the ingredients in these products, not on the dosage form. While an exception to a similar warning was made for lip balm products, that exception was made in part because lip balms are not only a solid dosage form, but are usually packaged in dispensing containers or holders that avoid all direct contact between the product and the hands. Antidandruff hair groom ointments are not packaged in a similar manner. The agency concludes, therefore, that the warning to avoid eye contact is justified for antidandruff hair groom ointments, and it is being proposed in this tentative final monograph.

24. One comment recommended that the warnings for coal tar products in proposed § 358.750(c)(2)(i) "Use caution in exposing skin to sunlight after applying this product. It may increase your tendency to sunburn for up to 24 hours after application" and § 358.750(c)(2)(ii) "Do not use this product in or around the rectum or in the genital area or groin except on the advice of a doctor" be applied only to products formulated for use on the body or for use as a hair groom. The comment argued that the warnings are inappropriate for shampoos which are applied only to the scalp and rinsed off within a few minutes. The comment also mentioned that the Panel had recommended that these warnings apply to "coal tar products for use on the body in the event that such products are included in the monograph" (47 FR 54659).

As the Panel stated in its report (47 FR 54657), coal tar has been shown to produce photosensitivity reactions. Although shampoos remain on the hair and scalp for a short exposure period, residual amounts of the drug will remain on the scalp and hair and could increase the likelihood of a photosensitive reaction. Therefore, the agency agrees with the Panel's recommended warning and it is being proposed in this tentative final monograph.

With respect to the second warning cautioning against use of the product in or around the rectum, genital area, or groin, the agency agrees that the warning is inappropriate for formulations intended to be applied and washed off after brief exposure (e.g.,

shampoos, preshampoo rinses, post shampoo rinses). Therefore, the warning cautioning against use of coal tar products in or around the rectum, genital area, or groin is being proposed in this tentative final monograph only for formulations of coal tar that are intended to be applied and left on the skin.

25. Several comments objected to the recommended warning in § 358.750(c)(3) for selenium sulfide-containing products, "Do not use if you have open sores on your scalp." One comment referred to the statement, "Comparatively little absorption occurs after local application of selenium sulfide to normal skin, but the drug is absorbed more readily from inflamed or damaged epithelium" (Ref. 1), which the Panel used to support the need for such a warning. The comment maintained that this statement is "virtually a truism," in that most drugs are more readily absorbed through damaged skin that intact skin. Therefore, the comment concluded there is no reason why selenium sulfide should be treated differently from any other antidandruff drug in this respect.

One comment stated that the warning is not necessary because the amount of selenium absorbed would not present a health hazard. The comment argued that the low selenium content in OTC dandruff shampoos, together with the short time the product is on the scalp before being rinsed off, would expose the consumer to only a minute fraction of the USDA Recommended Daily Allowance (RDA) for selenium of 50 to 200 mg/day. The comment added that the irritation caused by the contact of detergent in a shampoo with an open sore would discourage repeated application.

A reply comment agreed with the second comment above and also cited an unpublished study in which New Zealand rabbits showed no absorption of selenium above normal dietary levels after application of 2 ml per kg of 1 percent selenium sulfide to abraded and unabraded skin (Ref. 2). Selenium blood levels were measured before application of formulation and 30 minutes and 4 hours after application. The comment argued that millions of ounces of 1 percent selenium sulfide shampoo have been sold OTC since 1971, and that the only incidence of selenium toxicity in humans cited by the Panel was a report by Ransone et al. (Ref. 3) of one patient developing symptoms of selenium toxicity after using a prescription product containing 2.5 percent selenium sulfide in 1961. The comment maintained that there are no actual data to support such a warning and that conjecture alone, in the absence of factual evidence to the contrary, should not be sufficient to establish the need for an "open sore" warning statement on 1 percent selenium sulfide.

The agency has reviewed the data and arguments submitted by the comments. The agency acknowledges that there appears to be only one case report of selenium toxicity (Ref. 3), which occurred with a prescription product that was 2½ times more potent than the product covered by this rulemaking. In view of the widespread use of the one percent concentration product with no reports of selenium toxicity, the agency agrees with the comments that the warning in § 358.750(c)(3) cannot be justified for products containing 1 percent selenium sulfide. Therefore, the warning is not being included in this tentative final monograph.

References

(1) Swineyard, E.A., "Surface-Acting Drugs," *in* "The Pharmacologic Basis of Therapeutics," 5th Ed., edited by L.S. Goodman and A. Gilman, Macmillan Publishing Co., New York, p. 953, 1975.

(2) Study #TE78–502, Comment C00022, Docket No. 82N–0214, Dockets Management Branch.

(3) Ransone, J.W., N.M. Scott, and E.C. Knoblock, "Selenium Sulfide Intoxication," *New England Journal of Medicine*, 265: 384–385, 1961.

D. Comments on Combinations

26. Several comments noted the Panel's failure to establish a clear combination policy and requested the agency to recognize combinations of two ingredients from different therapeutic categories that are effective for the same condition. Two of the comments cited the General Guidelines for OTC Drug Combination Products dated September 1978 (Ref. 1), as support for their request that these combinations be allowed. The comments specifically asked that the combination of coal tar and salicylic acid for the treatment of psoriasis be recognized as Category I. One comment pointed out that although the mechanism of action for coal tar is not clearly knowm it is obviously different from that of salicylic acid. Thus, these two ingredients would clearly meet the general combination guidelines for ingredients from different therapeutic categories.

A number of comments also urged the agency to recognize combinations of ingredients from different therapeutic categories to treat different concomitant symptoms. The comments faulted the Panel for not allowing combinations of ingredients to treat dandruff, psoriasis, and seborrheic dermatitis with ingredients that provide symptomatic relief of dryness, itching, and inflammation frequently associated with these conditions. The comments requested that the agency recognize Category I antipruritics, for relief of itching, and Category I skin protectants, for relief of dry flaking skin, as rational combinations with Category I ingredients for the control and treatment of dandruff, seborrheic dermatitis, and psoriasis. The comments specifically requested the agency to recognize as Category I the following combinations: coal tar and salicylic acid; coal tar and hydrocortisone; coal tar and allantoin; coal tar and benzocaine; coal tar and menthol; sulfur and menthol; and coal tar, salicylic acid, and benzocaine.

The agency agrees with the comments that it is rational and consistent with the General Guidelines for OTC Drug Combination Products (Ref. 1) to allow ingredients from different therapeutic categories, to be combined to treat different concomitant symptoms. However, in the case of the combinations mentioned by the comments, the symptoms that would be treated by the various ingredients are not clearly different. For example, although an antipruritic could relieve the itching associated with dandruff, seborrheic dermatitis, or psoriasis, the dandruff/seborrheic dermatitis/psoriasis ingredients are also capable of relieving the same symptom.

The General Guidelines for OTC Drug Combination Products state that combination OTC drug products must also conform to the requirements of the general OTC drug regulations, specifically 21 CFR 330.10(a)(4)(iv), which require that each active ingredient in a combination make a contribution to the claimed effect. In the combinations mentioned by the comments, because the ingredients are capable of relieving the same symptoms, the contribution would need to be a demonstration that combination is somehow better than the individual ingredients used alone, e.g., the symptoms are relieved sooner, or the combination provides greater relief in reducing the severity of the symptoms.

The Panel did not find the data submitted to it to be adequate to establish general recognition of the effectiveness of such combinations, and the comments did not submit any additional data. Because the contribution of the ingredients in the combinations mentioned by the comments has not been adequately demonstrated, the agency is not including these combinations in the tentative final monograph.

References

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products," September 1978, Docket No. 78D–0322, Dockets Management Branch.

27. One comment objected to the Panel's conclusion that ". . . any combination product containing a Category II ingredient is Category II." The comment contended that agents listed as Category II single ingredients may possibly be more effective in combination and that the action of each agent may complement the other so that the resulting combination is safe and effective. The comment specifically asked for reconsideration of a combination of phenol and sodium chloride for psoriasis of the scalp so that this combination is not forced off the market.

The agency agrees with the comments that there may be circumstances in which an ingredient may not be appropriate for use as a single ingredient but may be appropriate in a combination product. Paragraph 5 of the agency's General Guidelines for OTC Drug Combination Products (Ref. 1) states: "In some cases an ingredient may be appropriate for use only in a specific combination or data may be available only to support the use of the ingredient in combinations but not as a single ingredient. In such cases the ingredient will be placed in Category I only in permissible combinations and not as a single ingredient."

With respect to the comment's request that the agency reconsider the classification of phenol and sodium chloride for psoriasis of the scalp, the agency notes that the data submitted to the Panel did not show any contribution of the sodium chloride to the combination of phenol and sodium chloride, nor were any additional data submitted with the comment. Should such data become available, the agency would consider classification of such a combination.

Reference

(1) Food and Drug Administration, "General Guidelines for OTC Drug Combination Products, September 1978," Docket No. 78D–0322, Dockets Management Branch.

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

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

1. Summary of Ingredient Categories

The agency has reviewed all claimed active ingredients submitted to the Panel, as well as other data and information available at this time, and has made some changes in the categorization of dandruff, seborrheic dermatitis, and psoriasis active ingredients recommended by the Panel. As a convenience to the reader, the following list is included as a summary of the categorization of dandruff, seborrheic dermatitis, and psoriasis active ingredients and uses recommended by the Panel and the proposed categorization by the agency.

CATEGORIZATION OF INGREDIENTS

Ingredient	Panel		Agency	
	Category	Uses [1]	Category	Uses
Alkyl isoquinolinium bromide.	III	D	III	D
Allantion	III	D, S, P	III	D, S, P
Benzalkonium chloride.	III	D	III	D
Benzethonium chloride.	III	D, C	III	D, C
Benzocaine	II	P	II	P
Borate preparations.	II	D, S	II	D, S
Captan	III	D	III	D
Chloroxylenol	III	D, S	III	D, S
Coal tar preparations.	I, III [2]	D, S, P	I	D, S, P
Colloidal oatmeal.	II	D	II	D
Cresol	II	P	II	P
Ethohexadiol	III	D	III	D
Eucalyptol	III	D	III	D
Hydrocortisone preparations.	III	D, S, P	I [3]	S, P
Juniper tar	III	D, S, P	III	D, S, P
Lauryl isoquinolinium bromide.	III	D	III	D
Menthol	III	D, S, P	III	D, S, P
Mercury oleate	II	P	II	P
Methylbenzethonium chloride.	III	C [4]	III	C
Methyl salicylate.	III	D	III	D
Phenol and phenolate sodium.	III	S, P	III	S, P
Pine tar preparations.	III	D, S, P	III	D, S, P
Providone-iodine.	III	D, S	III	D, S
Pyrithione zinc	I	D, S	I	D, S
Resorcinol	II	P	II	P
Salicylic acid	I	D, S, P	I	D, S, P
Selenium sulfide.	I	D	I	D, S
Sodium salicylate.	III	D, S	III	D, S
Sulfur	I	D	I	D
Thymol	III	D	III	D
Undecylenate preparations.	III	D, S, P	III	D, S, P

[1] C=Cradle cap, D=Dandruff, S=Seborrheic dermatitis, P=Psoriasis

[2] The Panel classified coal tar in Category I for use in a shampoo only and in Category III for other uses.

[3] Indications for hydrocortisone preparations for seborrheic dermatitis and psoriasis are being included in the rulemaking for OTC external analgesic drug products (See proposed rule published elsewhere in this issue of the Federal Register.) Hydrocortisone preparations remain in Category III for the treatment of dandruff.

[4] This tentative final monograph contains labeling for "cradle cap" even though no ingredients are included in Category I for this use at this time. In the event that new data submitted to the agency during the allotted 12-month comment and new data period are not sufficient to establish "monograph conditions" for this use, it will not be included in the final monograph.

2. Testing of Category II and Category III Conditions

Interested persons may communicate with the agency about the submission of data and information to demonstrate the safety or effectiveness of any dandruff, seborrheic dermatitis, and psoriasis ingredient or condition included in the review by following the procedures outlined in the agency's policy statement published in the **Federal Register** of September 29, 1981 (46 FR 47740) and clarified April 1, 1983 (48 FR 14050). That policy statement includes procedures for the submission and review of proposed protocols, agency meetings with industry or other interested persons, and agency communications on submitted test data and other information.

B. Summary of the Agency's Changes in the Panel's Recommendations

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

1. Because of the number of changes that have been made, as summarized below, many of the section and paragraph numbers have been redesignated in this tentative final monograph.

2. The agency has classified coal tar in Category I for use in dandruff, seborrheic dermatitis, and psoriasis and added the following warnings: (1) "Do not use for prolonged periods without consulting a doctor." (2) "Do not use this product with other forms of psoriasis therapy such as ultraviolet radiation or prescripion drugs unless directed to do so by a doctor." (See comment 5.)

3. The agency has proposed standards for coal tar preparations in this tentative final monograph. (See comment 7.)

4. The agency has changed the terms in the definitions section of the monograph and added additional information to better describe the conditions under consideration.

5. A seborrheic dermatitis indication has been proposed for selenium sulfide in the tentative final monograph. (See comment 8.)

6. The lower limit of the concentration range of pyrithione zinc in formulations intended to be applied and washed off after a brief exposure has been revised from 1 percent to 0.95 percent. The monograph also proposes that the concentration range for formulations

intended to remain on the scalp is 0.1 to 0.25 percent. (See comments 10 and 11.)

7. An indication for hydrocortisone for the symptomatic relief of seborrheic dermatitis and psoriasis is being proposed elsewhere in this issue of the **Federal Register** for inclusion in the rulemaking for OTC external analgesic drug products (21 CFR Part 348). Hydrocortisone is not being included in the rulemaking for OTC dandruff, seborrheic dermatitis, and psoriasis drug products to avoid duplication and overlap between rulemakings. (See comment 13.)

8. The agency has modified the indications statements to provide for greater flexibility in developing indications for the wide range of product formulations. Other allowable statements have been included in this tentative final monograph under the heading *Other Allowable Statements.* (See comment 16.)

9. The statement of identity for dandruff preparations has been changed to read "dandruff (insert product form)" or "antidandruff (insert product form)". The statements of identity for seborrheic dermatitis, psoriasis, and cradle cap products have been similarily revised. (See comment 17.)

10. The agency has clarified the directions for use in this tentative final monograph to accommodate the various dosage forms of dandruff, seborrheic dermatitis, and psoriasis drug products. (See comment 20.)

11. The agency has not included the warning "Do not use on children under two years of age except as directed by a doctor" in this tentative final monograph. (See comment 22.)

12. The agency has not included the warning "Do not use if you have open sores on your scalp" for selenium sulfide in this tentative final monograph. (See comment 25.)

13. In an effort to simplify OTC drug labeling, the agency proposed in a number of tentative final monographs to substitute the word "doctor" for "physician" in OTC drug monographs on the basis that the word "doctor" is more commonly used and better understood by consumers. Based on comments received to these proposals, the agency has determined that final monographs and any applicable OTC drug regulations will give manufacturers the option of using either the word "physician" or the word "doctor." This tentative final monograph proposes that option.

The agency has examined the economic consequences of this proposed rulemaking in conjunction with other rules resulting from the OTC drug review. In a notice published in the **Federal Register** of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this proposed rule for OTC dandruff, seborrheic dermatitis, and psoriasis drug products, is a major rule.

The economic assessment also concluded that the overall OTC drug review was not likely to have a significant economic impact on a substantial number of small entities as defined in the Regulatory Flexibility Act, Public Law 95–354. 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 dandruff, seborrheic dermatitis, and psoriasis drug products is not expected to pose such an impact on small businesses. Therefore, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

The agency invited public comment in the advance notice of proposed rulemaking regarding any impact that this rulemaking would have on OTC dandruff, seborrheic dermatitis, and psoriasis drug products. No comments on economic impacts were received. Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by November 28, 1986. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

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

Interested persons may, on or before September 29, 1986, submit to the Dockets Management Branch (HFA–305), Food and Drug Administration, Rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857, written comments, objections, or requests for oral hearing before the Commissioner on the proposed regulation. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before November 28, 1986. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register.**

Interested persons, on or before July 30, 1987, may also submit in writing new data demonstrating the safety and effectiveness of those conditions not classified in Category I. Written comments on the new data may be submitted on or before September 30, 1987. These dates are consistent with the time periods specified in the agency's final rule revising the procedural regulations for reviewing and classifying OTC drugs, published in the **Federal Register** of September 29, 1981 (46 FR 47730). Three copies of all data and comments on the data are to be submitted, except that individuals may submit one copy, and all data and comments are to be identified with the docket number found in brackets in the heading of this document. Data and comments should be addressed to the Dockets Management Branch (HFA–305) (address above). Received data and comments may also be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday.

In establishing a final monograph, the agency will ordinarily consider only data submitted prior to the closing of the administrative record on September 30, 1987. Data submitted after the closing of the administrative record will be reviewed by the agency only after a final monograph is published in the **Federal Register,** unless the Commissioner finds good cause has been shown that warrants earlier consideration.

List of Subjects in 21 CFR Part 358

OTC drugs; Corn and callus remover drug products; Dandruff, seborrheic dermatitis, and psoriasis drug products; Ingrown toenail relief drug products, Nailbiting and thumbsucking deterrent drug products; Pediculicide drug products; Skin bleaching drug products; and Wart remover drug products.

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, it is

proposed that Subchapter D of Chapter I of Title 21 of the Code of Federal Regulations be amended by adding a new Part 358 consisting at this time of Subpart H, to read as follows:

PART 358—MISCELLANEOUS EXTERNAL DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

Subpart H—Drug Products for the Control of Dandruff, Seborrheic Dermatitis, and Psoriasis

Sec.

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

Subpart H—Drug Products for the Control of Dandruff, Seborrheic Dermatitis, and Psoriasis

§ 358.701 Scope.

(a) An over-the-counter dandruff, seborrheic dermatitis, or psoriasis drug product in a form suitable for topical application 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.

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

§ 358.703 Definitions.

As used in this subpart:

(a) *Coal tar.* The tar used for medical purposes that is obtained as a byproduct during the destructive distillation of bituminous coal at temperatures in the range of 900° C to 1100° C. It may be further processed using either extraction with alcohol and suitable dispersing agents and maceration times or fractional distillation with or without the use of suitable organic solvents. The concentration of the coal tar portion of the final product should be in a relative concentration range of 0.5 to 5 percent coal tar.

(b) *Cradle cap.* Infantile seborrheic dermatitis.

(c) *Dandruff.* A condition involving an increase rate of shedding of dead epidermal cells of the scalp.

(d) *Psoriasis.* A condition of the scalp or body characterized by irritation, itching, redness, and extreme excess shedding of dead epidermal cells.

(e) *Seborrheic dermatitis.* A condition of the scalp or body characterized by irritation, itching, redness, and excess shedding of dead epidermal cells.

§ 358.710 Active ingredients for the control or dandruff, seborrheic dermatitis, or psoriasis.

The active ingredient of the product consists of any of the following within the specified concentration established for each ingredient:

(a) *Active ingredients for the control of dandruff.*

(1) Coal tar, 0.5 to 5 percent.

(2) Pyrithione zinc, 0.95 to 2 percent when formulated to be applied and then washed off after brief exposure.

(3) Pyrithione zinc, 0.1 to 0.25 percent when formulated to be applied and left on the skin or scalp.

(4) Salicylic acid, 1.8 to 3 percent.

(5) Selenium sulfide, 1 percent.

(6) Sulfur, 2 to 5 percent.

(b) *Active ingredients for the control of seborrheic dermatitis.*

(1) Coal tar, 0.5 to 5 percent.

(2) Pyrithione zinc, 0.95 to 2 percent when formulated to be applied and then washed off after brief exposure.

(3) Pyrithione zinc, 0.1 to 0.25 percent when formulated to be applied and left on the skin or scalp.

(4) Salicylic acid, 1.8 to 3 percent.

(5) Selenium sulfide, 1 percent.

(c) *Active ingredients for the control of psoriasis.*

(1) Coal tar, 0.5 to 5 percent.

(2) Salicylic acid, 1.8 to 3 percent.

§ 358.712 Active ingredients for the control of cradle cap. [Reserved]

§ 358.720 Permitted combinations of active ingredients.

Salicylic acid identified in § 358.710(a)(4) may be combined with sulfur identified in § 358.710(a)(6) provided each ingredient is present within the established concentration and the product is labeled for the control of dandruff.

§ 358.750 Labeling of drug products for the control of dandruff, seborrheic dermatitis, or psoriasis.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product with one or more of the following as appropriate:

(1) "Dandruff (insert product form)" or "antidandruff (insert product form)".

(2) "Seborrheic dermatitis (insert product form)".

(3) "Psoriasis (insert product form)".

(b) *Indications.* The labeling of the product states, under the heading "Indications," any of the phrases listed in this paragraph. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed below, may also be used, as provided in § 330.1(c)(2), subject to the provisions of section 502 of 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 relief of" or "Controls") "the symptoms of" (select one or more of the following, as appropriate: "dandruff," "seborrheic dermatitis," and/or "psoriasis.")

(2) The following terms may be used in place of the words "the symptoms of" in the indications in paragraph (1) of this section: ("skin" and/or "scalp," as appropriate) (select one or more of the following: "itching," "irritation," "redness," "flaking," "scaling,") "associated with").

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) *For products containing any ingredient identified in § 358.710.* (i) "For external use only."

(ii) "Avoid contact with the eyes—if this happens, rinse thoroughly with water."

(iii) "If condition worsens or does not improve after regular use of this product as directed, consult a doctor."

(2) *For any product containing coal tar identified in § 358.710(a), (b), or (c).* (i) "Use caution in exposing skin to sunlight after applying this product. It may increase your tendency to sunburn for up to 24 hours after application."

(ii) "Do not use for prolonged periods without consulting a doctor."

(3) *For products containing coal tar when formulated to be applied and left on the skin (e.g., creams, ointments, lotions).* "Do not use this product in or around the rectum or in the genital area or groin except on the advice of a doctor."

(4) *For products containing coal tar identified in § 358.710(c) for the control of psoriasis.* "Do not use this product with other forms of psoriasis therapy such as ultraviolet radiation or prescription drugs unless directed to do so by a doctor."

(5) *For products containing any ingredient identified in § 358.710(b) or*

(c) for the control of seborrheic dermatitis or psoriasis. "If condition covers a large area of the body, consult your doctor before using this product."

(d) *Directions.* The labeling of the product contains the following information under the heading "Directions". More detailed directions applicable to a particular product formulation may also be included.

(1) *For products containing active ingredients for the control of dandruff, seborrheic dermatitis, or psoriasis when formulated to be applied and then washed off after brief (a few minutes) exposure (e.g., shampoos, preshampoo rinses, postshampoo rinses).* "For best results use at least twice a week or as directed by a doctor."

(2) *For products containing active ingredients for the control of dandruff, seborrheic dermatitis, or psoriasis when formulated so as to be applied and left on the skin or scalp (e.g., creams, ointments, lotions, hairgrooms).* "Apply to affected areas one to four times daily or as directed by a doctor."

(3) *For products containing active ingredients for the control of seborrheic dermatitis or psoriasis of the skin when formulated as soaps.* "Use on affected areas in place of your regualr soap."

(e) The word "physician" may be substituted for the word "doctor" in any of the labeling statements in this section.

(f) *Other allowable statements.* The following phrases are considered truthful and nonmisleading and may be used elsewhere in the labeling in place of the term "For the relief of" or "Controls" in the indication statements identified in paragraph (b) of this section: "fights," "reduces," "helps eliminate," "helps stop," "controls recurrence of," "fights recurrence of," "helps prevent recurrence of," "reduces recurrence of," "helps eliminate recurrence of," "helps stop recurrence of."

§ 358.752 Labeling of drug products for the control of cradle cap.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as "cradle cap (insert product form)."

(b) *Indications.* The labeling of the product states, under the heading "Indications," the following: "Relieves scaly inflammation of the scalp associated with cradle cap." Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed above, may also be used, as provided in § 330.1(c)(2), subject to the provisions in section 502 of 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.

(c) *Warnings.* The labeling of the product contains the following warnings under the heading "Warnings":

(1) "For external use only."

(2) "Avoid contact with the eyes—if this happens, rinse thoroughly with water."

(3) "If condition worsens or does not improve after regular use of this product as directed, consult a doctor."

(d) *Directions.* [Reserved]

(e) The word "physician" may be substituted for the wold "doctor" in any of the labeling statements in this section.

Dated: May 3, 1986.

Frank E. Young,

Commissioner of Food and Drugs.

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21 CFR Part 348

[Docket No. 78N-0301]

External Analgesic Drug Products for Over-the-Counter Human Use; Amendment to Tentative Final Monograph

AGENCY: Food and Drug Administration.

ACTION: Further notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking in the form of an amended tentative final monograph that modifies the indications for which over-the-counter (OTC) hydrocortisone-containing external analgesic drug products are generally recognized as safe and effective and not misbranded, by adding an indication for use in the symptomatic treatment of seborrheic dermatitis and psoriasis. FDA is issuing this notice of proposed rulemaking after considering the report and recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products and public comments on the advance notice of proposed rulemaking for OTC dandruff, seborrheic dermatitis, and psoriasis drug products that was based on those recommendations. The agency's proposal concerning OTC dandruff, seborrheic dermatitis, and psoriasis drug products is being published elsewhere in this issue of the **Federal Register.** These proposals are part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments objections, or requests for oral hearing on the proposed regulation before the Commissioner of Food and Drugs by September 29, 1986. New data by July 30, 1987. Comments on the new data by September 30, 1987. These dates are consistent with the time periods specified in the agency's revised procedural regulations for reviewing and classifying OTC drugs (21 CFR 330.10). Written comments on the agency's economic impact determination by November 28, 1986.

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

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of December 4, 1979 (44 FR 69768), 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 external analgesic drug products, together with the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (Topical Analgesic Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these drug classes. Interested persons were invited to submit comments by March 6, 1980. Reply comments in reponse to comments filed in the initial comment period could be submitted by April 3, 1980.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC external analgesic drug products was published in the **Federal Register** of February 8, 1983 (48 FR 5852.)

In the **Federal Register** of December 3, 1982 (47 FR 54646), 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 dandruff, seborrheic dermatitis, and psoriasis drug products, together with the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products (Miscellaneous External Panel), which was the advisory review panel responsible for evaluating data on the active ingredients in these