DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 358

[Docket No. 82N-0214]

RIN 0905-AA06

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule in the form of a final monograph establishing conditions under which over-the-counter (OTC) dandruff, seborrheic dermatitis, and psoriasis drug products are generally recognized as safe and effective and not misbranded. FDA is issuing this final rule after considering public comments on the agency's proposed regulation, which was issued in the form of a tentative final monograph, and all new data and information on dandruff, seborrheic dermatitis, and psoriasis drug products that have come to the agency's attention. This final monograph is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: December 4, 1992.

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

SUPPLEMENTARY INFORMATION: In the **Federal Register** of 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 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 the **Federal Register** of February 8, 1983 (48 FR 5761), 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, after deletion of a small amount of trade secret information, were placed on display in the Dockets Management Branch (HFA-305), Food and Drug Administration, currently located in rm. 1-23, 12420 Parklawn Drive, Rockville, MD 20857.

The agency's proposed regulation, in the form of a tentative final monograph, for OTC dandruff, seborrheic dermatitis, and psoriasis drug products was published in the **Federal Register** of July 30, 1986 (51 FR 27346). Interested persons were invited to file by September 29, 1986, written comments, objections, or requests for oral hearing before the Commissioner of Food and Drugs regarding the proposal. Interested persons were invited to file comments on the agency's economic impact determination by November 28, 1986. New data could have been submitted until July 30, 1987, and comments on the new data until September 30, 1987.

In the **Federal Register** of October 1, 1986 (51 FR 35003), the agency advised that it had extended the comment period until October 29, 1986, on the proposed rulemaking, to allow for greater participation by interested persons. Final agency action occurs with the publication of this final monograph, which is a final rule establishing a monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products.

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

In the proposed regulation for OTC dandruff, seborrheic dermatitis, and psoriasis drug products (51 FR 27346), the agency advised that the conditions under which the drug products that are subject to this monograph will be generally recognized as safe and effective and not misbranded (monograph conditions) will be effective 12 months after the date of publication in the **Federal Register.** Therefore, on or after December 4, 1992, 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.

In response to the proposed rule on OTC dandruff, seborrheic dermatitis, and psoriasis drug products, six manufacturers, two trade associations, one medical association, and one health care professional submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (address above). Any additional information that has come to the agency's attention since publication of the proposed rule is also on public display in the Dockets Management Branch.

All "OTC Volumes" cited throughout this document refer to the submissions made by interested persons pursuant to the call-for-data 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 notice of proposed rulemaking. The volumes are on public display in the Dockets Management Branch.

I. The Agency's Conclusions on the Comments

A. General Comments

1. One comment contended that OTC drug monographs are interpretive, as opposed to substantive, regulations. The comment referred to statements on this issue submitted earlier to other OTC drug rulemaking proceedings.

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 at 9471 to 9472); in paragraph 3 of the preamble to the tentative final monograph for OTC antacid drug products, published in the **Federal Register** of November 12, 1973 (38 FR 31260); and in paragraph 1 of the preamble to the tentative final monograph in the present proceeding (51 FR 27346 at 27347). FDA reaffirms the conclusions stated in those documents. Court decisions have confirmed the agency's authority to issue substantive regulations by informal rulemaking. (See, e.g., *National Nutritional Foods Association* v. *Weinberger*, 512 F.2d 688, 696–698 (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. One comment recommended that any use of the word "dandruff" in labeling be limited only to drug products and not be allowed for cosmetic products. The comment contended that the description "remove(s) loose flakes of dandruff" will create an impression in the mind of the consumer that the product being used is designed to mitigate or treat a disease, and thus is a drug. Two other comments contended that references to dandruff, if allowed, on cosmetic shampoos can lead to consumer confusion. The comments disagreed with the following statement in the proposed rule:

> * * * 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. * * * 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. (See 51 FR 27346 at 27347.)

The comments requested the agency to reconsider its position "that the mere use of the word 'dandruff' does not automatically render a shampoo a drug." In support of their requests, the comments provided the results of a survey (Ref. 1) that assessed 100 consumers' interpretations of the statement "Shampoo X removes loose flakes of dandruff and clears the hair of dandruff flakes or scales." The target audience was an equal number of men and women, aged 18 to 54 years, who used a dandruff shampoo for the control of dandruff in the past year. Based on the question asked, 71 percent of the responders stated that the product "is an antidandruff shampoo," 72 percent considered it to be "a dandruff treatment," and 76 percent stated it "controls dandruff." On the negative side, 52 percent felt that the product would not "prevent dandruff." The comments contended that the results of the survey showed that consumers overwhelmingly interpreted the removal of dandruff flakes as synonymous with "antidandruff," "dandruff control shampoo," and "dandruff treatment." The comments concluded that the survey shows that the type of claims being allowed for "cosmetic shampoos" actually describe antidandruff OTC drug products.

A fourth comment argued that the results of the consumer survey do not support the argument that claims referring solely to a product's effectiveness in cleaning the hair, a traditional cosmetic claim, are also claims that the product is effective for drug purposes. The comment argued that a consumer survey may provide some evidence of how consumers interpret a particular advertising or labeling claim, but it is not determinative of the regulatory status of the product making that claim.

The comment contended that the consumer survey had a number of defects and, thus, its results are unreliable. The comment described in detail the purported defects in the study. The comment also stated that the claim presented to the consumers was that the shampoo "cleared the hair," not "cleaned the hair," of dandruff flakes. The comment argued that the word "clear" suggests a more permanent and more drug-like effect and that the researcher's choice of terminology may have skewed the results. The comment concluded that the survey did not show that consumers perceive the shampoo to have clear-cut therapeutic effects that treat a pathologic condition, because the survey never asked that precise question.

Another comment raised issues about the validity of the methodology of the survey. These issues included whether "control" questions should have been used to screen out certain respondents, whether screening questions were neutral, whether terms should have been defined for the respondents, whether any effort should have been made to ascertain the consumers' understanding of certain terms, and whether the researcher's choice of terminology may have influenced the results.

In the tentative final monograph, the agency stated that when the use of the term "dandruff" deals only with appearance and not with the treatment or prevention of the underlying disease condition, such as a statement that a product removes loose flakes of dandruff or cleans the hair of dandruff flakes or scales, the product is a cosmetic (51 FR 27346 at 27348). In the survey mentioned above, consumers were asked to interpret the statement "Shampoo X removes loose flakes of dandruff and clears the hair of dandruff flakes or scales." The agency considers each clause of this statement to be a cosmetic claim, because removal of loose flakes and clearing the hair are actions of cleansing, beautifying, or promoting attractiveness within the definition of cosmetic in section 201(i) of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 321(i)). As stated in the tentative final monograph, 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 render the product a drug (51 FR 27346 at 27348). As discussed in comment 3 below, dandruff removal products can be drugs, cosmetics, or both.

References

(1) Shampoo Product Statement Study, Kornhauser and Calene, Inc., October 1986, in Comment C00031, Docket No. 82N–0214, Dockets Management Branch.

3. One comment disagreed with the agency's position of prohibiting cosmetic claims from appearing in any portion of the labeling that is required by the monograph. The comment stated that so long as the labeling is truthful and not misleading, the joint placement of information about both the cosmetic and drug claims of a product should be permitted anywhere on the labeling. The comment contended that although dandruff, seborrheic dermatitis, and psoriasis are medical conditions treated with drug products, these products may also have important cosmetic functions. For example, a dandruff shampoo may have a cleansing or shampoo (cosmetic) function, and a relief of itching, flaking and scaling (drug) function. The comment argued that consumers need both kinds of information and urged the agency to expressly allow the joint placement of drug and cosmetic claims in a dandruff, seborrheic dermatitis, and psoriasis product used both as a drug and as a cosmetic. The comment contended that if this information were to appear on entirely different portions of the label, consumers could be confused and misled as to what the product will do. The comment requested that the following language be added to all relevant final regulations: "The

agency emphasizes that OTC drug monographs do not pertain to cosmetic terminology contained on such products and do not preclude in any way the use of truthful and nonmisleading cosmetic terminology in the labeling of cosmetic/drug products."

A final OTC drug monograph covers 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 do 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 OTC drug monograph as well as applicable cosmetic labeling requirements.

In addition to the indications allowed for OTC dandruff, seborrheic dermatitis, and psoriasis 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 revised labeling requirements for OTC drug products (21 CFR 330.1(c)(2)), it is the agency's position that cosmetic claims may not appear within the boxed area designated "APPROVED USES." As discussed at 51 FR 16264 (paragraph 14), cosmetic terminology is not reviewed and approved by FDA in the OTC drug monographs and therefore could not be placed in the box. 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 2(iii) for labeling cosmetic/drug products.

The agency does not disagree with the comment's statement that consumers need both drug and cosmetic information about these products. However, the agency does not agree that if the drug and cosmetic information appears in different places in the labeling consumers would necessarily be confused or misled. The agency believes the manner in which the information is presented, as well as its location, is important to consumer understanding.

Although the agency does not specifically prohibit commingled drug and cosmetic labeling (other than in the Indications section), the agency believes that information about the product's claims should be appropriately described so that consumers will be readily able to differentiate the drug and cosmetic aspects of the labeling. If commingled drug and cosmetic labeling claims are confusing or misleading, the product's labeling may be misleading within the meaning of the act and the product misbranded under sections 502(a) or 602(a) of the act. This position is consistent with that stated in the final rule for OTC topical acne drug products published in the **Federal Register** of August 16, 1991 (56 FR 41008 at 41017). Accordingly, the agency is not adding the comment's suggested language to this final monograph.

4. One comment stated that the Miscellaneous External Panel limited its review of OTC dandruff, seborrheic dermatitis, and psoriasis drug products to determining which ingredients are safe and effective for "controlling" these conditions and ignored the symptomatic relief that may or may not be related to treatment of the condition. The comment interpreted the definitions for OTC drug products that "control" dandruff, seborrheic dermatitis, and psoriasis to include those having only symptomatic relief and/or those having curative action.

The Panel stated (47 FR 54646 at 54653), and the agency agrees, that OTC drugs for dandruff, seborrheic dermatitis, and psoriasis do not cure, but with regular use at best can only control or relieve the symptoms of these conditions. The indications for the use of these products in § 358.750(b) of this final monograph clearly establish that they are used to "control" or "relieve the symptoms of" dandruff, seborrheic dermatitis, and psoriasis. The terms "relief" or "control" are used synonymously to describe the action of the products. The indications state that the product's action is on the symptoms of the condition or describe the symptoms as itching, irritation, redness, flaking, and scaling associated with dandruff, seborrheic dermatitis, and psoriasis.

5. One comment suggested that the monograph provide for the use of emollients and/or lubricants in the treatment of psoriasis. In support of its position, the comment cited statements from a reference discussing treatment of psoriasis: "The simplest forms of treatment—lubricants * * * should be tried first * * *" and "Lubricating creams, hydrogenated vegetable (cooking) oils, or white petrolatum are applied * * * while the skin is still damp after bathing" (Ref. 1). The comment added that these materials are classified as emollients in another textbook and are described as fats or oils used for their local action on the skin (Ref. 2). Stating that the use of such ingredients is widely regarded as a safe, effective, economical means of treating psoriasis, the comment complained that none of those types of ingredients have been included in the tentative final monograph. The comment further contended that because of demonstrated problems and expense of one or more "active" ingredients listed in the tentative final monograph, the public is poorly served by the omission of emollients from the monograph.

The agency has no basis on which to grant the comment's request. No data were submitted with the textbook statements in support of the use of an emollient and/or lubricant in the treatment of psoriasis. If adequate supporting data are submitted to the agency in the form of a petition to amend the final monograph, the monograph could be amended to include emollients and/or lubricants.

References

(1) Berkow, R., editor, "The Merck Manual of Diagnosis and Therapy," 14th ed., Merck Sharp and Dohme Research Laboratories, Rahway, NJ, p. 2054, 1982.

(2) Swinyard, 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. 947, 1975.

B. Comments on Active Ingredients

6. One comment suggested that any product containing boric acid or its salt approved for OTC use be labeled "not for use in children," "not for use on broken or severely irritated skin," and/or "for topical use only." The comment stated that boric acid poisoning has been reported after accidental ingestion or from absorption through the skin (Ref. 1).

The Panel concluded that borate preparations are not safe, and data were lacking to permit their final classification as effective for OTC topical use for controlling dandruff or seborrheic dermatitis (47 FR 54646 at 54667). In response to the Panel's report, one comment requested a reevaluation of the Panel's conclusions, and called attention to a 2-year feeding study on rats and dogs that was not considered by the Panel. The agency reviewed all available data on borates, including the reports of other panels. Based upon that reevaluation, the agency concluded in the tentative final monograph that there was ample evidence to support the safety of up to 1 percent borates for OTC topical use in dandruff and seborrheic dermatitis preparations, but that the effectiveness of borates for the treatment of those conditions has not been demonstrated (51 FR 27346 at 27351). No additional effectiveness studies were submitted. Accordingly, boric acid and sodium borate were included in a final rule published in the

Federal Register of November 7, 1990 (55 FR 46914 at 46917) that listed certain OTC active ingredients that are not generally recognized as safe and effective. (See 21 CFR 310.545(a)(7).) Thus, there is no need at the present time to further consider inclusion of the comment's requested labeling in this monograph.

Reference

(1) Rubenstein, A. D., and D. M. Musher, "Epidemic Boric Acid Poisoning Simulating Staphylococcal Toxic Epidermal Necrolysis of the Newborn Infant: Ritters Disease," The Journal of Pediatrics, 77:884–887, 1970.

7. One comment inquired whether there is any evidence that chloroxylenol is effective as a topical antifungal agent. Referring to a discussion in the tentative final monograph (51 FR 27346 at 27351) that the Advisory Review Panel on Antimicrobial II Drug Products had concluded that chloroxylenol is safe for OTC use as a topical antifungal, the comment noted that there was no discussion of effectiveness.

The issue raised in the tentative final monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products only concerned the safety of chloroxylenol. In another OTC drug rulemaking, the Advisory Review Panel on Antimicrobial II Drug Products concluded that there were insufficient data available to permit final classification of the effectiveness of chloroxylenol for OTC topical antifungal use (47 FR 12480 at 12533). A study submitted in response to the Panel's report on topical antifungal drug products was inadequate to show effectiveness, and in the tentative final monograph for OTC antifungal drug products, chloroxylenol remained in Category III for effectiveness (54 FR 51136 at 51139).

The Miscellaneous External Panel evaluated chloroxylenol for controlling dandruff and seborrheic dermatitis (47 FR 54646 at 54672 to 54673). The Panel recognized one theory that dandruff is caused by *Pityrosporum ovale* (a yeast-like fungus resident to the scalp) (47 FR 54651 and 54653). However, based on the submitted studies, the Panel stated that chloroxylenol was shown to have an antimicrobial effect on selected bacteria, but it had little or no effect on fungi and yeast (47 FR 54673). The Panel concluded, therefore, that additional data are needed to demonstrate the effectiveness of chloroxylenol for controlling dandruff and seborrheic dermatitis. The agency did not receive any submissions of effectiveness data on chloroxylenol in response to the Panel's report or the tentative final monograph. Therefore, chloroxylenol was also included with those OTC drug active ingredients not generally recognized as safe and effective in 21 CFR 310.545(a)(7). (See comment 6 above).

8. One comment agreed with the definition and concentration limits proposed for coal tar in § 358.703(a) of the tentative final monograph, i.e., 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. Noting that a variety of coal tar solutions and fractions are used in OTC dandruff, seborrheic dermatitis, and psoriasis drug products, the comment contended there should be a labeling requirement to state the actual coal tar equivalent concentration contained in any coal tar solution, derivative, or fraction. As an example, the comment stated that a preparation containing a 10-percent solution of coal tar U.S.P. would be listed as "10 percent LCD (2 percent Coal Tar U.S.P. equivalent)." The comment concluded that this approach would allow consumers to compare "apples with apples" when comparing two coal tar-containing preparations.

The agency agrees with the comment that information concerning the coal tar equivalent concentration is useful and would allow consumers to be able to evaluate the comparative strengths of coal tar-containing drug products. Although section 502(e) of the act requires statement of the active ingredient in the labeling of OTC drug products, it only requires labeling of quantitative information for a number of named ingredients and their derivatives, alcohol, and prescription drugs. Agency regulations in 21 CFR 1.21(a)(1) provide that labeling of a drug shall be deemed misleading if it fails to reveal facts that are "material in light of other representations made or suggested by statement, word, design, device or any combination thereof." Other agency regulations in 21 CFR 201.10(c) state that "the labeling of a drug may be misleading by reason (among other reasons) of: * * * (2) Failure to reveal the proportion of, or other fact with respect to, an ingredient present in such drug, when such proportion or other fact is material in the light of the representation that such ingredient is present in such drug."

In the case of coal tar, the agency believes that, without the equivalent concentration of coal tar appearing in the product's labeling, the labeling could be misleading. Accordingly, the agency is requiring in this final monograph that the labeling of OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis state the equivalent concentration of coal tar contained in any coal tar solution, derivative, or fraction used as the source of the coal tar in the product. The concentration for coal tar in this final monograph will now read as follows in § 358.710(a)(1), (b)(1) and (c)(1): "Coal tar, 0.5 to 5 percent. When a coal tar solution, derivative, or fraction is used as the source of the coal tar, the labeling shall specify the identity and concentration of the coal tar source used and the concentration of the coal tar present in the final product."

The comment described a product named LCD. LCD is an abbreviation for Liquor Carbonis Detergens, which is Coal Tar Topical Solution, U.S.P. (Ref. 1). This solution is a 20-percent solution of coal tar in alcohol. The product described by the comment would be labeled as follows: "Contains 10 percent of coal tar topical solution, equivalent to 2 percent coal tar." The determination of the coal tar concentration in the final product is made as follows: When 10 percent of a final product constitutes Coal Tar Topical Solution, U.S.P., that means that the final product contains 10 percent of the U.S.P. solution (20% coal tar), or 2 percent coal tar. The coal tar topical solution appears in the labeling as the actual active ingredient used in the product, while the equivalent coal tar percentage tells the user of the product the actual amount of coal tar that is present.

Reference

(1) "The United States Pharmacopeia XXII—The National Formulary XVII," The United States Pharmacopeial Convention Inc., Rockville, MD, p. 341, 1989.

9. One comment strongly recommended that hydrocortisone in OTC drug products not be increased above 0.5 percent. The comment stated that as a manufacturer of hydrocortisone creams it was aware that dermatologists are reporting seeing many patients who could have "run into trouble" from use of 0.5 percent hydrocortisone. The comment contended that increasing the strength of OTC hydrocortisone above 0.5 percent would create an even greater safety problem. Another comment also recommended that 1 percent hydrocortisone not be included in OTC drug products in any form.

In the **Federal Register** of July 30, 1986 (51 FR 27360), the agency deferred hydrocortisone from the rulemaking for OTC dandruff, seborrheic dermatitis, and psoriasis drug products to the rulemaking for OTC external analgesic drug products. At that time, the agency amended the tentative final monograph for OTC external analgesic drug

products to add seborrheic dermatitis and psoriasis to the list of conditions for which hydrocortisone is 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 (51 FR 27363). Since the comments were submitted, the agency published another amendment of the tentative final monograph on OTC external analgesic drug products on February 27, 1990 (55 FR 6932), in which it proposed to increase the concentrations for OTC hydrocortisone and hydrocortisone acetate from the current levels of 0.25 to 0.5 percent to from 0.25 to 1 percent. The agency's proposal to switch above 0.5 to 1 percent hydrocortisone to OTC marketing status was based on an extensive review of safety data. The comments did not present any evidence that 0.25 to 1 percent concentrations were potentially unsafe. The one comment did not provide any specific information about the types of problems with hydrocortisone that are being reported by dermatologists. However, the agency has received numerous comments to the proposal that was published in the **Federal Register** of February 27, 1990. After these comments have been evaluated, the agency's final determination on OTC use of hydrocortisone above 0.5 up to 1 percent will be stated in a future issue of the **Federal Register**, as part of the rulemaking for OTC external analgesic drug products.

10. One comment noted that the Panel classified povidone-iodine in Category I for safety but in Category III for effectiveness (47 FR 54646 at 54679), and the agency proposed the same classification in the tentative final monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products because no comments on povidone-iodine were received in response to the Panel's recommendation (51 FR 27346 at 27357). The comment contended that manufacturers did not conduct research on povidone-iodine in support of its effectiveness in the treatment of dandruff, seborrheic dermatitis, and psoriasis because of business reasons and not because other available evidence suggested that povidone-iodine would be ineffective for such use.

The comment was concerned that povidone-iodine's nonmonograph status in this rulemaking could be interpreted as an indication of its general ineffectiveness for other indications. The comment requested that, if povidone-iodine remains nonmonograph at the final rule stage because no data were submitted in support of its effectiveness, the preamble should state that povidone-iodine was not included in the final monograph because no effectiveness data were submitted, and that such data could be submitted with a petition to amend the final monograph pursuant to 21 CFR 330.10(a)(12).

The agency notes that no data on the effectiveness of povidone-iodine for use in OTC dandruff, seborrheic dermatitis, and psoriasis drug products were submitted following publication of the tentative final monograph. Accordingly, povidone-iodine was also included with those OTC drug active ingredients not generally recognized as safe and effective in 21 CFR 310.545(a)(7). (See comment 6 above.) As the comment noted, new data on the ingredient's effectiveness for this use may be submitted in the form of a petition to amend the final monograph.

The agency is unable to state why manufacturers did not submit data on this ingredient in the present rulemaking. The nonmonograph status of povidone-iodine for dandruff, seborrheic dermatitis, and psoriasis uses has no bearing on its status in other OTC drug monographs.

11. One comment requested that the final monograph include 0.3 percent pyrithione zinc in a rinse-off product for the control of dandruff. The comment included summaries of five double-blind, placebo-controlled clinical studies (Ref. 1) previously submitted in a new drug application to support the efficacy of 0.3 percent pyrithione zinc in a rinse-off conditioner for the control of dandruff. Studies DA-134, DA-137, and DA-157 were conducted using the "original" formulation of the rinse-off product, and studies DA-186 and DA-187 were conducted using a reformulated vehicle for the product.

Study DA-134 was a double-blind, parallel group trial involving 430 female subjects having dandruff in at least one of eight designated areas of the scalp. Subjects with seborrheic dermatitis or atopic dermatitis were excluded. Subjects were stratified according to age and initial dandruff grade, and were randomly assigned to one of the following treatment regimens: placebo lotion shampoo followed by 0.3 percent pyrithione zinc conditioner, 1.0 percent pyrithione zinc lotion shampoo followed by placebo conditioner, 1.0 percent pyrithione zinc lotion shampoo followed by 1.0 percent conditioner, or placebo lotion shampoo followed by placebo conditioner. Subjects used their assigned products ad libitum for 6 weeks, and were evaluated for amount of adherent dandruff at 3 and 6 weeks after initiation of treatment. Statistical analysis of the results showed that all three active treatment regimens were significantly more effective than the placebo regimen ($p=0.05$), but were not significantly different from each other. Irritation was reported by two subjects on the 1.0 percent pyrithione zinc shampoo plus 1.0 percent pyrithione zinc conditioner regimen.

Study DA-137 was a double-blind, parallel group trial involving 600 female subjects having dandruff in at least 1 of 8 designated areas of the scalp. Subjects with seborrheic dermatitis or atopic dermatitis were excluded. Subjects were stratified according to age and initial dandruff severity, and were randomly assigned to one of the following treatment regimens: 2.0 percent pyrithione zinc lotion shampoo followed by placebo conditioner, placebo shampoo followed by 1.5 percent pyrithione zinc conditioner, placebo shampoo followed by 1.0 percent pyrithione zinc conditioner, placebo shampoo followed by 0.3 percent pyrithione zinc conditioner, or placebo shampoo followed by placebo conditioner. Subjects used their assigned products ad libitum for 6 weeks, and were evaluated for amount of adherent dandruff at 3 and 6 weeks after initiation of treatment. Statistical analysis of the results showed that all active treatment regimens were significantly more effective than the placebo regimen ($p=0.05$). The regimen of placebo shampoo followed by 1.0 percent pyrithione zinc conditioner was significantly more effective than 2.0 percent pyrithione zinc lotion shampoo followed by placebo conditioner. The results from using the three conditioners did not differ significantly from each other. Irritation was reported by nine subjects, but only one of these was in the group using placebo shampoo plus 0.3 percent pyrithione zinc conditioner.

Study DA-157 was a double-blind, parallel group trial involving 660 male and female subjects having dandruff in at least one of eight designated areas of the scalp. Subjects with seborrheic dermatitis or atopic dermatitis were excluded. Subjects were stratified according to age, sex, shampoo frequency, and dandruff severity, and were randomly assigned to one of the following treatment regimens: 1.0 percent pyrithione zinc lotion shampoo followed by 0.3 percent pyrithione zinc conditioner, 1.0 percent pyrithione zinc lotion shampoo followed by placebo conditioner, placebo lotion shampoo followed by 0.3 percent pyrithione zinc

conditioner, placebo lotion shampoo followed by placebo conditioner, 1.0 percent selenium sulfide shampoo followed by 0.3 percent pyrithione zinc conditioner, or 1.0 percent selenium sulfide shampoo followed by placebo conditioner. Subjects used their assigned product ad libitum for 6 weeks, and were evaluated at 3 and 6 weeks after initiation of treatment. Statistical analysis of the results showed that all active treatment regimens were significantly more effective than placebo ($p=0.05$). The combination of 1.0 percent selenium sulfide shampoo plus 0.3 percent pyrithione zinc conditioner was significantly more effective than the other treatment regimens ($p=0.05$). The results from the remaining regimens did not differ significantly from each other. Irritation was reported by seven subjects on various regimens. One of these was in the group using 1.0 percent selenium sulfide shampoo plus 0.3 percent pyrithione zinc conditioner, while none were in the group using placebo shampoo plus 0.3 percent pyrithione zinc conditioner.

Study DA–186 was a randomized double-blind, parallel group trial involving 345 male and female subjects having a total dandruff score of eight or higher on a scale of 0 to 80. For grading, the scalp was divided into eight sections, and each section was graded for dandruff on a scale of 0 to 10. Subjects with eczema, seborrheic dermatitis, or psoriasis were excluded. Subjects were randomly assigned to one of the following treatment groups: placebo shampoo with placebo conditioner, placebo shampoo with the reformulated vehicle 0.3 percent pyrithione zinc conditioner, or placebo shampoo with the approved vehicle 0.3 percent pyrithione zinc conditioner. Subjects used their assigned products ad libitum, but at least twice a week for 6 weeks, after which they were again graded for dandruff severity. There were no significant differences among the three treatment groups in the initial mean dandruff scores. The final mean dandruff scores did not differ significantly between the group using the reformulated conditioner and the group using the approved conditioner. Scores in both groups were significantly lower than in the group using placebo conditioner ($p=0.05$). No adverse reactions were reported with the reformulated conditioner.

Study DA–187 was a double-blind, parallel group trial involving 500 male and female subjects having a total dandruff score of eight or higher as evaluated by the procedure described above for study DA–186. Subjects were randomly assigned to one of the following treatment groups: Placebo shampoo with placebo conditioner, pyrithione zinc shampoo with placebo conditioner, or pyrithione zinc shampoo with the reformulated vehicle 0.3 percent pyrithione zinc conditioner. Subjects used their assigned products at least twice a week for 6 weeks, after which they were again graded for dandruff severity. There were no significant differences among the three treatment groups in the initial mean dandruff scores. The final mean dandruff scores did not differ significantly between the group using the active shampoo with reformulated 0.3 percent pyrithione zinc conditioner and the group using the active shampoo with placebo conditioner. Scores in both groups were significantly lower than in the group using placebo shampoo with placebo conditioner ($p=0.05$). Adverse reactions were reported by two subjects using the active shampoo/reformulated conditioner regimen. These were itchy scalp in one, and a patchy rash on the face and neck in the other. Both reactions cleared by one week after discontinuance. One subject on the active shampoo/placebo conditioner regimen also developed a rash on the neck, which resolved by 1 week after discontinuance.

Based upon the above studies, the agency concludes that 0.3 percent pyrithione zinc as a rinse-off product is safe and effective for OTC use in the control of dandruff. In the tentative final monograph, the agency proposed pyrithione zinc as Category I for the relief of the symptoms of dandruff when formulated at 0.95 to 2 percent to be applied and then washed off after brief exposure (51 FR 27346 at 27359). In this final monograph, the agency is revising the lower limit for pyrithione zinc in a rinse-off product for the control of dandruff to 0.3 percent. (The lower limit for pyrithione zinc in rinse-off products for the control of seborrheic dermatitis remains at 0.95 percent.) The agency's detailed comments and evaluation of the above studies are on file in the Dockets Management Branch (Ref. 2).

References

(1) Comment No. RPT2, Docket No. 82N–0214, Dockets Management Branch.

(2) Letter from W. E. Gilbertson, FDA, to F. L. Spadini, The Procter and Gamble Co., coded LET9, Docket No. 82N–0214, Dockets Management Branch.

12. One comment requested the inclusion of a micronized form of selenium sulfide at a concentration of 0.6 percent in § 358.710 (a) and (b) of the final monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products. The comment provided data from five studies (Ref. 1) intended to demonstrate safety and effectiveness of 0.6 percent micronized selenium sulfide in the control of dandruff and seborrheic dermatitis. The comment stated that the selenium sulfide used in the studies met the USP XXI specifications (Ref. 2) and has an additional particle size specification of not less than 90 percent under 7 microns and an average particle size of not more than 2 microns.

The agency has reviewed the comment and other information and determined that the data are insufficient to establish the effectiveness of 0.6 percent micronized selenium sulfide in the treatment of dandruff and seborrheic dermatitis. The five clinical studies submitted by the comment include the following:

(a) *Protocol CP–CA83.* This study was a double-blind comparison of the efficacy of 0.6 percent micronized selenium sulfide, 1 percent nonmicronized selenium sulfide, and shampoo vehicle in treating dandruff symptoms. Each subject was instructed to use a nonantidandruff shampoo during a wash-out period for 2 weeks in order to eliminate the effect of previously used antidandruff shampoos. One hundred sixteen subjects with a total dandruff score of 21 or higher (maximum of 40, minimum of zero) were admitted to the study. One hundred fourteen subjects, 15 Caucasian males and 99 Caucasian females, completed the study. Of these 114 subjects, several were excluded from the efficacy analysis as their total dandruff scores were considered unevaluable.

Subjects were instructed to shampoo twice weekly throughout the study; they were blinded as to which shampoo they received during the treatment period. Dandruff was assessed (prior to shampooing once every other week) by an investigator who, presumably, had no knowledge of the treatment assigned.

Baseline comparability of treatment groups for categorical variables (i.e., sex, hair length, and scalp condition) was evaluated in this study using a chi-square test. In addition, baseline comparability of treatment groups for continuous variables (i.e., age and total baseline dandruff score) was evaluated with a one-way analysis of variance. The agency considers the statistical evaluation submitted to be acceptable for the type of data collected.

The baseline comparability tests showed that the treatment groups were demographically highly compatible to one another. The mean scores within each treatment group appeared to be independent of sex for the baseline and

for the three treatment weeks, although the issue of sex effect within group remained statistically inconclusive because of the small sample size.

On the basis of the data provided, the mean reduction of total dandruff scores from baseline was statistically significantly greater (at the 10 percent level or less) in the subjects using 0.6 percent micronized selenium sulfide than in the placebo following 2, 4, and 6 weeks of their treatment ($p=0.023$, $p=0.062$, $p<0.001$, respectively).

A statistically significant difference in mean reduction scores between 1 percent nonmicronized selenium sulfide and shampoo vehicle was also noted following 2, 4, and 6 weeks of treatment ($p=0.023$, $p=0.017$, and $p<0.001$, respectively). There was no significant difference in the mean reduction score between 0.6-percent micronized selenium sulfide and 1-percent nonmicronized selenium sulfide following 2, 4, and 6 weeks of treatment ($p=0.958$, $p=0.550$, and $p=0.832$, respectively).

Both the 0.6-percent micronized and the 1-percent nonmicronized selenium sulfide showed statistically significantly more rapid improvement than the shampoo vehicle ($p=0.002$ and $p=0.004$, respectively). There was no significant difference between improvement rates of 0.6 percent micronized and 1 percent nonmicronized selenium sulfide ($p=0.832$). The sample size appeared to be adequate for each treatment group involved.

These data and the protocol design indicate that the 0.6 percent micronized selenium sulfide is statistically more effective than the shampoo vehicle and is statistically as effective as the active control (1 percent nonmicronized selenium sulfide). The study is a well-controlled clinical trial that has used the proper tests for statistical analysis.

(b) *Protocol 84–050.* This study was a comparison of the antidandruff efficacy of a shampoo containing 1 percent nonmicronized selenium sulfide with a shampoo containing either 0.6 percent or 1 percent micronized selenium sulfide.

One hundred sixty-one subjects who met the minimum dandruff score criterion described in the previous study were selected for admission to this study. The subjects, mostly Caucasians, were randomized into the three treatment groups after having used a nonantidandruff shampoo for 2 weeks and were instructed to shampoo twice weekly for 4 weeks. An assessment of the subjects' dandruff condition was made weekly.

The analytical procedures used in this study were generally similar to those employed in the previous study (Protocol CP–CA83). There were no statistical indications that the three treatment groups differed in age, sex, race, hair length, or scalp condition. At the end of the 4-week treatment period, about 30 percent of the subjects using each formulation in the study were found to have a dandruff score of 0 (no measurable dandruff). There was no significant difference in the mean reduction of dandruff scores from baseline between any two treatment groups ($p>0.15$), nor was there any significant difference in the mean improvement rates between any two treatment groups ($p>0.82$). All three treatments were found to be statistically equally effective. The sample size appeared to be adequate for each treatment group involved.

Although FDA regulations allow the use of active controls as a comparison group, the agency does not consider this study to be a well-controlled clinical trial for the following reasons: (1) There appears to be no acceptable explanation for the substantial difference in the effect of treatment time (2 weeks vs. 6 weeks) between this and the previous study (Protocol CP–CA83) for treatment with 0.6 percent micronized selenium sulfide, when the product used in each study was manufactured by the same company; (2) placebos were not included in the test; and (3) there appear to be no ethical reasons why placebos should not have been included in the study. Had the study shown that the treatment with 0.6 percent micronized selenium sulfide was statistically more effective than the other two treatments instead of equally effective, the design bias would have been less. The agency considers that the use of an active control alone in this situation violates the principle of having a double-blind study, because, in theory, all the investigator has to do is to deliberately, as well as indiscriminately, give lower dandruff scores to each subject gradually over time to yield favorable results.

(c) *Protocol CP–CA70.* This study was a double-blind comparison of the antidandruff efficacy of a shampoo containing 0.6 percent micronized selenium sulfide to a shampoo containing 1-percent nonmicronized selenium sulfide and to a shampoo vehicle.

Both the mean dandruff reduction scores and the mean improvement rate obtained from this study for 0.6 percent micronized selenium sulfide were highly consistent with those found in the study using Protocol CP–CA83 but not with those in the study using Protocol 84–050, especially when the observations from the study using Protocol CP–CA83 were confined to the first four weeks of treatment only. However, the results indicate that all three treatments (including the shampoo vehicle) were statistically equally ineffective in treating dandruff symptoms ($p>0.24$). This study was a well-designed controlled clinical trial which apparently did not distinguish the efficacy of 0.6 percent micronized selenium sulfide from that of the shampoo vehicle.

(d) *Protocol 82–028.* This study on 103 subjects compared antidandruff efficacy of shampoos containing 0.2 percent micronized selenium sulfide, 0.4 percent micronized selenium sulfide, 0.6 percent micronized selenium sulfide, and 0.2 percent micronized selenium sulfide plus 0.5 percent polyethyleneimine.

This study was, by design, a dose-searching type clinical trial which included neither a placebo nor an FDA-approved active control. For this reason, this study cannot be considered a well-designed controlled trial.

(e) *Protocol 81–013.* This study compared, under randomized and, presumably, double-blind conditions, the antidandruff efficacy of a shampoo containing 0.2 percent micronized selenium sulfide with a shampoo containing 1 percent nonmicronized selenium sulfide. Based on the design, the agency finds this study irrelevant because it did not involve the testing of 0.6 percent micronized selenium sulfide.

In summary, only two of the studies (Protocol CP–CA83 and Protocol CP–CA70) can be regarded as well-designed controlled clinical trials. Of these two, the latter study failed to demonstrate that 0.6 percent micronized selenium sulfide was statistically more effective than the shampoo base.

Although the study using Protocol 84–050 was able to show that the 0.6-percent micronized formulation was statistically equal in effectiveness in reducing dandruff as the 1-percent nonmicronized formulation, it was not a well-controlled trial by design for several reasons: this study yielded noticeably lower dandruff scores (and hence higher improvement rates as well) than those obtained by other investigators; this study did not include a placebo; and the active control used was a product manufactured by the same company, which was not demonstrated to be less effective than 0.6 percent micronized selenium sulfide. Although this study appears to show efficacy of the drug, its result cannot outweigh the uncertainty produced by the diverse results from the two vehicle-controlled studies.

In the study using Protocol CP–CA83, there were fewer assessments made on the treatments than statistically desired. In addition, the effect of treatment time for micronized or nonmicronized selenium sulfide was found to be substantially different from (worse than) that observed in the study using Protocol 84–050, the latter study including neither a placebo nor a more convincing active control. For the above reasons, at least one additional well-controlled study of adequate sample size is needed to support the efficacy of 0.6 percent micronized selenium sulfide. The additional study should include a placebo and have more frequent dandruff assessments made over an established followup period.

No data were submitted to demonstrate efficacy of 0.6 percent micronized selenium sulfide in treating seborrheic dermatitis. Data from separate studies are needed.

Regarding specifications for micronized selenium sulfide, there should be a particle size specification for the selenium sulfide active ingredient which includes both a lower and an upper limit. For example, 90 percent of particles should be less than 10 microns; 99 percent should be less than 20 microns; no particles should be greater than 20 microns.

On the basis of the submitted data, the agency is unable to propose at this time that 0.6 percent micronized selenium sulfide be Category I for the treatment of dandruff and seborrheic dermatitis.

The agency's detailed comments and evaluation of the above studies are on file in the Dockets Management Branch (Ref. 3).

References

(1) Comment No. LET007, Docket No. 82N–0214, Dockets Management Branch.

(2) "United States Pharmacopeia XXI—National Formulary XVI," United States Pharmacopeial Convention, Inc., Rockville, MD, p. 958, 1984.

(3) Letter from W. E. Gilbertson, FDA, to M. Haney, Ross Laboratories, Coded ANS001, Docket No. 82N–0214, Dockets Management Branch.

C. Comments on Combinations

13. Several comments contended that, in addition to the permitted combination proposed in § 358.720, there are a number of dandruff, seborrheic dermatitis, and psoriasis active ingredients that could be rationally combined with other active ingredients to treat the same condition or different concomitant symptoms. Two of the comments referred to the general regulations for OTC drug combination products in 21 CFR 330.10(a)(4)(iv), which state:

> An OTC drug may combine two or more safe and effective active ingredients and may be generally recognized as safe and effective when each active ingredient makes a contribution to the claimed effect(s); when combining of the active ingredients does not decrease the safety or effectiveness of any of the individual active ingredients; and when the combination, when used under adequate directions for use and warnings against unsafe use, provides rational concurrent therapy for a significant proportion of the target population.

Two comments mentioned the agency's statement in the tentative final monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products (51 FR 27346 at 27356) 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.

The comments suggested adding a section to the final monograph that would read as follows:

> Any active ingredient identified in §§ 358.712 and 358.720 may be combined with one or more active ingredients from §§ 352.10 and 352.20 [sunscreen], §§ 347.10 and 347.20 [skin protectant], and §§ 348.10 and 348.20 [external analgesic] drug monographs; provided that: (1) Each active ingredient is present in full therapeutic doses, or subtherapeutic doses where a subtherapeutic dose is appropriate; (2) the product is safe and is effective individually for each of the indications intended from the combination; and (3) the product contains adequate statements of identity, indications, directions for use, and warnings consistent with each therapeutic category represented by an active ingredient in the combinations, or, in the case in which a particular therapeutic use is limited in dose or duration of treatment, to prominently display only the most conservative limitations, e.g., not to be used for more than 7 days.

The comments urged the agency to consider possible rational OTC combinations available with dandruff, seborrheic dermatitis, and psoriasis products, and to add language specifically addressing such potential combinations. One comment noted that the manufacturer of the product would be responsible for demonstrating that its individual combination is both safe and effective for each indication prior to distribution, as stated in 21 CFR 330.10(a)(4)(iv).

Stating that combinations from different therapeutic categories that are effective for the same conditions should be allowed, two comments suggested that menthol (antipruritic) and coal tar (antidandruff) could be combined to treat different concomitant symptoms (itching and dandruff). The comments contended that menthol provides immediate relief of itching, while coal tar may also incidentally relieve itching in conjunction with its slower-acting antidandruff effect. Thus, the comments suggested that the combination, while relieving one of the same symptoms, acts by different mechanisms and at different time intervals. One of the comments submitted data to show the antipruritic effect of menthol when combined with a shampoo containing coal tar. (See comment 14 below.)

One of the comments contended that dandruff, seborrheic dermatitis, and psoriasis are disease states that form a continuum and that they share the symptoms of flaking and hyperproliferation. Noting that the agency proposed salicylic acid and sulfur as a Category I combination drug product for the control of dandruff, the comment urged that the indications for that combination be extended to include seborrheic dermatitis and psoriasis of the scalp.

The comment also contended that by proposing to amend the tentative final monograph for OTC external analgesic drug products to include claims for hydrocortisone-containing external analgesics for the relief of itching of seborrheic dermatitis and psoriasis (51 FR 27360 at 27363), the agency has recognized this type of product as safe and effective for this use. The comment claimed that "other external analgesic active ingredients, either alone or in combination with active ingredients of this monograph, are also of value in the treatment or control of dandruff, seborrheic dermatitis, or psoriasis, since itching is a common symptom associated with these conditions." The comment claimed that the Panel's consideration of only the antidandruff action of specific ingredients led to the omission of recommendations for rational combinations. The comment maintained that for this category of drug products, there are a number of rational combinations with other active ingredients which should be allowed by FDA under 21 CFR 330.10(a)(4)(iv). The comment requested monograph status for the following combinations:

(a) Sunscreen and dandruff, seborrheic dermatitis, or psoriasis ingredient.

(b) Skin protectant or external analgesic and keratolytic ingredient (e.g., salicylic acid and/or coal tar).

(c) External analgesic (e.g., menthol, benzocaine, and others) and dandruff ingredient.

(d) External analgesic (e.g., menthol, benzocaine, and others) and psoriasis ingredient.

(e) Keratolytic (e.g., salicylic acid) and psoriasis ingredient.

(f) Keratolytic (e.g., salicylic acid), external analgesic (e.g., menthol, benzocaine, and others), and psoriasis or dandruff ingredient.

(g) Sun protectant, keratolytic, and dandruff, psoriasis, or seborrheic dermatitis ingredient.

(h) Skin protectant, external analgesic (e.g., menthol, benzocaine, and others), and psoriasis or seborrheic dermatitis ingredient.

(i) Skin protectant, sun protectant, and psoriasis ingredient.

(j) Skin protectant and psoriasis ingredient.

Another comment claimed that coal tar, salicylic acid, and benzocaine should be placed in Category I for the treatment of psoriasis without further testing. The comment explained that coal tar reduces the number and size of epidermal cells, decreasing epidermal proliferation and dermal infiltration; salicylic acid loosens the scales enabling them to be washed off; and benzocaine acts immediately to prevent itching, thus helping to prevent scratching. This combination, the comment contended, is a rational combination of ingredients from different therapeutic categories to treat different concomitant symptoms.

One comment requested that the agency provide for combinations of any analgesic, anesthetic, and antipruritic active ingredient for relief of itching in § 348.10 and any active ingredient for the control of dandruff or seborrheic dermatitis in § 358.710 (a) and (b). The comment requested, in the event that the agency does not allow such combinations, that the tentative final monograph specifically be changed to provide for the combination of selenium sulfide 1 percent identified in § 358.710(a)(5) and menthol 0.1 to 1 percent identified in § 348.10(b)(6) for the treatment of the symptoms listed in the respective tentative final monographs relative to control of dandruff, seborrheic dermatitis, and itching. The comment stated that selenium sulfide 1 percent is not known to have inherent antipruritic properties but that clinical studies previously submitted to the Panel demonstrate that relief of itching appears to be related to alleviating the underlying condition. The comment further stated that menthol's antipruritic action is based on its ability to depress cutaneous sensory receptors, which is independent and unrelated to selenium sulfide's ability to relieve itching by alleviating the underlying medical condition.

One comment claimed the agency has recognized a role for "rational concurrent therapy" by requiring a warning in § 358.750(c)(2)(i) for products containing coal tar, which reads: "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." The comment stated that a Category I combination product containing sunscreen and antidandruff, seborrheic dermatitis, or psoriasis ingredients would provide that need.

The agency agrees that there are instances where it would be rational and consistent with the General Guidelines for OTC Drug Combination Products (Ref. 1) to have ingredients from different therapeutic categories combined to treat different concomitant symptoms. The comments identified numerous combinations that they considered rational and potentially beneficial to consumers. For example, it is possible that certain sunscreen ingredients could be combined with certain dandruff, seborrheic dermatitis, and psoriasis ingredients, e.g., to counteract the photosensitivity effect of coal tar, but the agency is not aware of any products being marketed for such use. There might also be benefit in combining an external analgesic ingredient (e.g., menthol or benzocaine) with certain dandruff, seborrheic dermatitis, and psoriasis ingredients, such as coal tar or selenium sulfide. However, no supportive data were submitted for any of the combinations requested except for menthol and coal tar. (See comment 14 below.) Although some of the combinations requested seem feasible, the agency has no data to determine which combinations are supportable and actually provide a concomitant benefit. As discussed in the tentative final monograph for this rulemaking (51 FR 27346 at 27356), combination OTC drug products must conform to the requirements of the general OTC drug regulations, specifically 21 CFR 330.10(a)(4)(iv), which requires that each active ingredient makes a contribution to the claimed effect. In the absence of data establishing that this contribution is made, these combinations are considered nonmonograph in this final rule. However, if adequate data are submitted to the agency in the form of a citizen petition to amend the final monograph (see 21 CFR 330.10(a)(12)), specific combinations could be included in the final monograph at a later date.

Reference

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

14. One comment contended that the combination of coal tar and menthol for the treatment of dandruff, seborrheic dermatitis, and psoriasis is a rational combination. The comment claimed menthol acts by quickly increasing the blood supply to the scalp and thus provides an almost immediate anti-itch effect, while coal tar has a slower-acting antidandruff effect. The comment pointed out that menthol and coal tar belong to different therapeutic categories (antipruritic and antidandruff, respectively) and are treating concomitant symptoms (itching and dandruff). The comment mentioned that antidandruff ingredients only incidentally relieve itching. The comment stated that the ingredients, while relieving the same symptoms, act by different mechanisms at different time intervals. The comment concluded that the combination should be placed in Category I without further testing. Subsequently, the comment submitted data (Ref. 1) in support of the effectiveness of a shampoo drug product for OTC use containing a combination of 9 percent coal tar and 1.5 percent menthol for relieving scalp itching associated with dandruff.

The agency has reviewed the submission and determined that the data do not demonstrate that the combination product offers any advantage over the single ingredients alone. Thus, the agency finds that the data are inadequate to support the inclusion of the combination product in the final monograph for OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis.

The clinical study conducted was designed to demonstrate the antipruritic action of a shampoo containing a combination of 9 percent coal tar and 1.5 percent menthol as compared to a shampoo containing 9 percent coal tar. In the tentative final monograph (51 FR 27346 at 27356; July 30, 1986), the agency stated that combination drugs with ingredients capable of relieving the same symptoms (itching, in this case) would need to demonstrate that "the combination is somehow better than the individual ingredient used alone, e.g., the symptoms are relieved sooner, or the combination provides greater relief in reducing the severity of the symptoms."

The clinical study was randomized and double-blind with parallel groups using either a single-dose of 9 percent coal tar solution with 1.5 percent

menthol or 9 percent coal tar solution. After a 4-day wash-out period (no shampoo permitted), subjects with (1) a diagnosis of dandruff with moderate to very severe scaling rated by a dermatologist; and (2) an associated degree of itching of at least moderate intensity (>50 on a 100 millimeter (mm) analog scale) rated by the subject were randomly allocated into one of the two treatment groups. Eighty-two subjects were enrolled but two of them were excluded from the efficacy analysis for violation of inclusion criteria (insufficient baseline scalp itch). At 5, 15, 30, and 60 minutes after treatment, the subjects were asked to evaluate antipruritic efficacy using a Control of Itching 100-mm visual analog scale by placing a line on the scale between "not at all" and "very much" in response to the question "How much did the shampoo help to control your scalp itching?" The subjects were also asked to rate relief of itching on a 6-point scale: 0=no relief, 1=slight relief, 2=mild relief, 3=moderate relief, 4=considerable relief, 5=complete relief.

The agency found that the study had a number of major defects:

The comparison of the combination product to coal tar results in an efficacy evaluation of the effect of menthol only. No rationale was offered for the failure to compare the combination product with 1.5 percent menthol. Thus, the contribution of coal tar to the combination product was not assessed.

With only one dose being administered to the subject, the antipruritic effect of regular use of the combination product by the general population having dandruff cannot be assessed.

The comment claimed that the two study medications were identical in aroma. However, menthol is a substance with a peppermint-like odor and at a concentration of 1.5 percent is considered a topical counterirritant in § 348.12(b) of the tentative final monograph for OTC external analgesic drug products (48 FR 5852 at 5868; February 8, 1983). Menthol is listed as an irritant that produces a cooling sensation. As the Topical Analgesic Panel noted in its evaluation of menthol as a counterirritant, when applied topically menthol produces a preliminary feeling of coolness followed by a sensation of warmth (44 FR 69768 at 69828). The comment did not say how the peppermint-like odor and the cooling sensation were blinded. Further, in § 348.10(b)(6) of the tentative final monograph for OTC external analgesic drug products, the analgesic, anesthetic, and antipruritic concentration of menthol is listed as 0.1 to 1 percent, while the concentration in the study submitted was 1.5 percent.

There are several indications that the protocol was not followed carefully. The protocol planned to include 40 males and 40 females in the study, but actual distribution was 31 males and 49 females.

There was an inconsistency in the protocol and the actual conduct of the study with respect to the efficacy evaluation. The protocol itself was inconsistent as to what outcome variable should be measured. Three types of measurement were to be assessed by subjects during the study as follows:

(a) Degree of itching—subjects would be asked to rate the degree of itching they are experiencing by placing a mark on a 100 mm analog scale whose ends represented:

Doesn't itch _____

Itches a lot _____

(b) Control of itching—subjects would be asked to respond to the question "How much did the shampoo help to control your scalp itching?" by designating a position on a 100 mm analog scale between:

Not at all _____

Very much _____

(c) Relief of itching—subjects would be asked to rate their relief by circling the phrase that best describes their relief at that moment:

Complete relief
Considerable relief
Moderate relief
Mild relief
Slight relief
No relief

According to the protocol, the degree of itching was to be evaluated both prior to treatment and immediately after treatment and also at 5, 15, 30, and 60 minutes after treatment. Control of itching was to be evaluated immediately after treatment. Relief of itching was to be evaluated at each time point. In the actual conduct of the study, no evaluation was made immediately after treatment for any of the three types of measurements, and no evaluation was made after treatment for the degree of itching. Furthermore, at 5, 15, 30, and 60 minutes after treatment, ratings of control of itching and relief of itching were made. The statistical methodology section of the protocol stated that itching would be evaluated as the difference and percent difference from baseline of itching at each time point. It is evident from this statement that the degree of itching, not control of itching, was intended for efficacy evaluation. Because the degree of itching was not evaluated after treatment, no efficacy evaluation of this parameter could be made.

The comment's analyst used analysis of variance techniques for both control of itching (analog scale) and relief of itching (categorical scale) at each time point and as the sums weighted by the time intervals between observations. Because the ordered responses of relief of itching are discrete and may not be normally distributed, FDA performed nonparametric techniques for this outcome variable. The p-values that FDA determined by Wilcoxon Rank Sum tests are presented in the third column of the table below whereas p-values as determined by the comment's analyst are listed in the second column.

RESULTS FOR RELIEF OF ITCHING (CATEGORICAL RESPONSES)

Time	p-value (ANOVA)	p-value (Wilcoxon Rank Sum)
	(Comment)	(FDA)
5 minutes	0.04	0.08
15 minutes	0.02	0.04
30 minutes	0.01	0.01
60 minutes	0.12	0.14
Overall sum of relief	0.04	0.06

It is FDA's view that for the relief of itching the nonparametric methods are preferred to ANOVA tests because the normality assumption may not apply to an outcome variable with limited integer ranges. FDA determined that the overall sum of relief using Wilcoxon Rank Sum test has a p-value of 0.06 compared to the p-value of 0.04 from the ANOVA tests done by the comment's analyst. The p-value for overall sum of control of itching is 0.08.

In comparing the comment's results for control of itching and FDA's analysis of those results using the Wilcoxon Rank Sum tests (see table above), only at 30 minutes does the comment's result for control of itching ($p = 0.04$) and FDA's analysis of relief of itching ($p = 0.01$) indicate a significant difference at the 5-percent level. At all other time intervals and for the overall sum, either the comment's results, FDA's analyses, or both do not show a significant difference at the 5-percent level. The results at 60 minutes (the comment's control of itching $p = 0.20$ and FDA's analysis of relief of itching $p = 0.14$) are particularly unimpressive.

The agency concludes that the study results do not demonstrate that the combination of coal tar and menthol is better than coal tar used alone for relief of scalp itch associated with dandruff. Two items raise specific questions about the clinical relevance of the reduction in itching:

(1) The time course of product use when compared to the study design; and

(2) The finding that any effect found tended to weaken by 60 minutes.

Based on the above, the combination of coal tar and menthol is not being included in this final rule for OTC dandruff, seborrheic dermatitis, and psoriasis drug products. The agency's detailed comments are on file in the Dockets Management Branch (Ref. 2). After publication of this final rule, an appropriate citizen petition with any additional data on the combination of coal tar and menthol may be filed requesting an amendment to the final rule (see 21 CFR 10.30).

References

(1) Comment No. RFT, Docket No. 82N-0214, Dockets Management Branch.

(2) Letter from W.E. Gilbertson, FDA, to J.R. Jacobs, Whitehall Laboratories, coded LET010, Docket No. 80N-0214, Dockets Management Branch.

15. One comment contended that salicylic acid in combination with coal tar should be recognized as Category I, stating that the mechanism of action for the two ingredients is different and therefore the ingredients complement each other. The comment explained that salicylic acid (a keratolytic) is "exfoliative, loosening the scales and removing the scurf," while coal tar is not exfoliative, does not aid in the removal of crusted scurf, and is antipruritic and antiseptic, thus preventing the return of dandruff. The comment concluded that a combination of the two ingredients provides a valuable product in the treatment of any itching and scaling condition such as dandruff, seborrheic dermatitis, and psoriasis.

Another comment submitted a proposed clinical protocol to evaluate the effectiveness of a combination of 2 percent coal tar and 2 percent salicylic acid in the treatment and control of scalp psoriasis (Ref. 1). The comment noted that in the advance notice of proposed rulemaking for these products, the Panel stated that for this combination, as well as other combinations listed, "appropriately designed studies must demonstrate that each of the active ingredients contributes to the claimed effect" (47 FR 54646 at 54682).

Neither comment provided data to support the effectiveness of the combination product. The proposed clinical protocol describes a 6-week, randomized, multicenter, double-blind, parallel-group comparison of 2 percent coal tar, 2 percent salicylic acid, and a combination containing 2 percent coal tar and 2 percent salicylic acid in the treatment of scalp psoriasis. The agency recommended that a four-arm study, which includes the vehicle, would be preferable to the three-arm study proposed by the comment. The agency's comments and evaluation of the protocol are on file in the Dockets Management Branch (Ref. 2).

The agency has not received any results from the clinical study described above nor any other data to support the effectiveness of the combination of 2 percent coal tar and 2 percent salicylic acid. Accordingly, this combination is not included in this final monograph. Publication of this final monograph, however, does not preclude future testing. Data in support of the above combination may be submitted via a citizen petition requesting an amendment of the monograph. (See 21 CFR 330.10(a)(12).)

References

(1) Comment No. 00035, Docket No. 82N-0214, Dockets Management Branch.

(2) Letter from W.E. Gilbertson, FDA, to M.S. Wortzman, Neutrogena Corporation, coded LET 006, Docket No. 82N-0214, Dockets Management Branch.

D. Comments on Labeling

16. One comment maintained that the large number of monograph warning and direction statements plus other general information required for OTC drugs (e.g., the statement of identity, general overdose warnings, net weight declarations, and lists of inactive ingredients) could impact adversely on the size of OTC drug packages and could significantly diminish the important and intended purpose of advice to the consumer on the safe and effective use of the products.

The agency concludes that all of the warnings and directions included in this final monograph are essential to ensure consumers' proper and safe use of OTC dandruff, seborrheic dermatitis, and psoriasis drug products. This information needs to appear on these OTC drug products regardless of the size of the container. In those instances where an OTC dandruf, seborrheic dermatitis, or psoriasis drug product is packaged in a container that is too small or otherwise unable to include all the required labeling, the product can be enclosed in a carton or be accompanied by a package insert that contains the information complying with the monograph. The labeling provisions in Part 201 (e.g., §§ 201.10(i), 201.15, 201.60, 201.61, and 201.62) address various requirements for labeling drugs including drugs packaged in containers too small to accommodate a label with sufficient space to bear all the information required for compliance with various regulations. In those instances where an OTC dandruff, seborrheic dermatitis, or psoriasis drug product is packaged in a container that is too small to include all of the required labeling, the product can be enclosed in a carton or be accompanied by a package insert that contains the information complying with the monograph. Manufacturers are also encouraged to print a statement on the product container label, carton, or package insert suggesting that the consumer retain the carton or package insert for complete information about the use of the product when all the required labeling does not appear on the product label.

The Nonprescription Drug Manufacturers Association has recently promulgated guidelines for industry to consider when examining product labels for readability and legibility. (Ref. 1) These guidelines are designed to assist manufacturers in making the labels of OTC drug products as legible as possible. The agency commends this voluntary effort and urges all OTC drug manufacturers to examine their product labels for legibility.

Reference

(1) "Label Readability Guidelines." The Nonprescription Drug Manufacturers Association, Washington, copy included in OTC Volume 06ATFM. Docket No. 78N-0038, Dockets Management Branch.

17. One comment claimed that the agency's proposed warning statements and label directions for dandruff, seborrheic dermatitis, and psoriasis drug products in § 358.750(c) and (d) are redundant, inapplicable, and often

contradictory. The comment contended that this information would confuse consumers rather than aid safe use of these products.

As an example, the comment cited the general warning statement for all products in § 358.750(c)(1)(iii), "If condition worsens or does not improve after regular use of this product as directed, consult a doctor," and argued that it does not include an acceptable duration of use before a consumer should obtain professional advice. The comment contended that this general warning statement was redundant when used with the proposed warning for products containing coal tar in § 358.750(c)(2)(ii) that states: "Do not use for prolonged periods without consulting a doctor."

The agency disagrees with the comment's general statement that the proposed warnings and label directions are redundant, inapplicable, and often contradictory in nature. The agency further disagrees that the warnings and directions information would confuse consumers and would not aid in the safe use of these products. The warnings and directions information was developed after an extensive review by the Panel and an extensive agency evaluation of the Panel's recommendations and the public comments submitted thereto.

Regarding the warning for all OTC dandruff, seborrheic dermatitis, and psoriasis drug products in § 358.750(c)(1)(iii), the agency concludes that it is appropriate to advise consumers to consult a doctor if the condition worsens or does not improve after using the product as directed. A warning of this type is used for many different types of OTC drug products. It is intended to ensure that more severe dermatologic conditions that do not respond to treatment with OTC drug products are treated by a doctor.

As discussed in comment 19 below, the agency is aware that coal tar has been associated with skin cancer but is not aware of any well-defined, long-term studies that show specifically how long coal tar products can be used without significant side effects. Although the agency has no basis to specify a definite time period for consumers to use coal tar products before consulting a doctor, the warning about prolonged use of coal tar products in § 358.750(c)(2)(ii) is not redundant with the general warning in paragraph (c)(1)(iii). Accordingly, the agency is including both warnings in this final monograph.

18. Referring to the warning proposed in § 358.750(c)(1)(ii), one comment contended that the statement, "Avoid contact with the eyes—if this happens, rinse thoroughly with water," is poorly worded both grammatically and stylistically. The comment suggested the following alternative: "Avoid contact with the eyes. If any gets into the eyes, rinse thoroughly with warm water."

The agency agrees that a slight change in wording similar to the comment's suggestion would improve the language style. The agency notes that the comment has included the word "warm" in the warning to describe the type of water that should be used to rinse the eyes. However, the comment did not provide any reason for this change. The agency is not aware of any reason to specify that "warm" water must be used. Therefore, the agency is not including the word warm in this warning which will appear in § 358.750(c)(1)(ii) of this final monograph as follows: "Avoid contact with the eyes. If contact occurs, rinse eyes thoroughly with water."

19. One comment stated that the warnings proposed in § 358.750(c)(1)(iii) (general warning for all products) and (c)(2)(ii) (specific warning for products containing coal tar) are too vague and leave the manufacturers of these products open to liability suits. The warnings state "If condition worsens or does not improve after regular use of this product as directed, consult a doctor," and "Do not use for prolonged periods without consulting a doctor." The comment requested that the agency include specific time periods in these warnings.

The agency recognizes that the warnings referred to by the comment are nonspecific as to how long the consumer may use OTC drug products for control of dandruff, seborrheic dermatitis, and psoriasis before consulting a doctor. However, the agency believes that the warnings, as stated, adequately alert the consumer of the precautions necessary when using these products. As discussed in the tentative final monograph for these products (51 FR 27346 at 27348 and 27349), two long-term studies using coal tar for the treatment of psoriasis showed no significant difference in development of skin cancer in the test group when compared to the expected incidence in selected populations of the United States. The length of time for use of coal tar products after initial treatment, in one of these studies, varied from no use up to as much as 26 years. The agency is not aware of any well defined, long-term studies that show specifically how long these products can be used without significant side effects. Therefore, the agency has no basis to specify a definite time period over which to use these products before consulting a doctor. The comment did not provide any information or data to indicate a specific time limit is necessary nor did it explain how these warnings leave manufacturers open to liability suits. Accordingly, the warnings proposed in § 358.750(c)(1)(iii) and (c)(2)(ii) are being included in this final monograph without revision.

20. One comment contended that the proposed warning statements in § 358.750(c)(1)(iii), "If condition worsens or does not improve after regular use of this product as directed, consult a doctor," and in § 358.750(c)(2)(ii), "Do not use for prolonged periods without consulting a doctor," are contradictory to several proposed directions. The comment cited the following directions in § 358.750: (d)(1) applicable to washoff products (e.g., shampoos, pre- and postshampoo rinses): "For best results use at least twice a week or as directed by a doctor;" (d)(2) applicable to leave-on products (e.g., creams, ointments, lotions, hairgrooms): "Apply to affected areas one to four times daily or as directed by a doctor;" and (d)(3) applicable to soap products for control of seborrheic dermatitis or psoriasis of the skin: "Use on affected area in place of your regular soap."

The agency disagrees with the comment's contention that the two warnings are contradictory to the directions in § 358.750(d)(1), (d)(2), and (d)(3). The directions instruct the consumer on the proper use of the products, while the warnings state precautions to be taken by those using the products. The directions in § 358.750(d)(1) and (d)(2) instruct the consumer on the frequency of using the product, and the direction in § 358.750(d)(3) instructs the consumer to use the OTC drug product in place of regular soap to assure that the active ingredient is re-applied regularly rather than intermittently with regular soap. The warning in § 358.750(c)(1)(iii) for all OTC dandruff, seborrheic dermatitis, and psoriasis drug products, on the other hand, is necessary to alert the consumer to seek professional help when warranted. An individual's sensitivity or allergic reaction to an OTC drug product could result in the condition worsening, and a misdiagnosed or unusually severe case of dandruff, seborrheic dermatitis, or psoriasis could result in no improvement after self-treatment. In these situations, it is important for the consumer to seek professional help. Further, the warning in § 358.750(c)(2)(ii) for coal tar containing products is important because the condition may not be amenable to self-treatment, and prolonged use of coal tar containing substances may not be entirely risk-free

due to the possible carcinogenic effects that may result after prolonged use. (See comment 19 above.)

21. One comment noted that the warning regarding the use of dandruff products on children under 2 years of age, which was recommended by the Panel in § 358.750(c)(1)(iv), was not included in the tentative final monograph. Noting that the warning has value, the comment stated that it will continue using the warning whether the monograph requires it or not.

The Panel's recommended warning was not included in the tentative final monograph (51 FR 27346 at 27355) in response to several comments urging its deletion. The comments had argued that the warning was unwarranted and unnecessary for dandruff control products, and the agency agreed.

The agency stated in the tentative final monograph that children under 2 years of age are not normally subject to dandruff and do not customarily use these products. The agency added that the margin of safety for dandruff control drug products is sufficiently great that the occasional exposure of young children to these products should not constitute any major medical problem. The comment did not submit any data to show that the warning is necessary. The agency concludes that it is not necessary to include a warning against using dandruff control products on children under 2 years of age in this final monograph.

The agency notes the comment's desire to continue using this warning even though the final monograph does not require it. As long as the required monograph warnings and directions appear on the product's label, the agency has no objection to the information described by the comment also appearing in some other portion of the label. Such information, however, may not appear in any portion of the labeling that is required by the monograph and may not appear in the boxed area or under the designation "APPROVED INFORMATION" provided for in 21 CFR 330.1(c) (2) (i).

22. One comment contended that the warning in § 358.750(c) (2) (i) regarding exposure to sunlight after applying coal tar products is inappropriate for washoff products used on the scalp or for hair grooming products which are used by persons with enough hair to protect them from the sun. This warning states: "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."

The agency considers this warning to be necessary both for washoff hair products and for other hair grooming products that contain coal tar. As discussed in the tentative final monograph (51 FR 27346 at 27355), coal tar has been shown to produce photosensitivity reactions. Because residual amounts of coal tar remain on the scalp, hair, and surrounding areas (e.g., neck) after using a washoff product (e.g., shampoo or rinse), the likelihood of photosensitivity occurring is increased. Although hair on the scalp gives some protection from the sun, the degree of protection is related to the amount of hair an individual has. Further, the skin surrounding the scalp is not protected by hair. Therefore, the agency is requiring the warning in § 358.750 (c) (2) (i) to protect consumers by alerting them to be careful about exposure to sunlight after applying any coal tar-containing products.

23. One comment contended that the proposed directions in § 358.750(d) (3) applicable to soap products for the control of seborrheic dermatitis or psoriasis of the skin, which state "Use on affected areas in place of your regular soap," are contradictory to the proposed warning statement in § 358.750(c) (5), "If condition covers a large area of the body, consult your doctor before using this product." In contrast, the comment mentioned that the warning for leave-on coal tar-containing creams, ointments, and lotions in § 358.750(c) (3), "Do not use this product in or around the rectum or in the genital area or groin except on the advice of a doctor," is not required for coal tar-containing soap products that are washed off, even if used in the bath for prolonged soaking periods.

The agency does not believe the directions in § 358.750(d) (3) are contradictory to the warning in § 358.750(c) (5). The agency believes that consumers with seborrheic dermatitis or psoriasis covering a large area of the body should consult a doctor before using these products in any form (e.g., soaps, ointments, etc.). The warning in § 358.750(c)(3) applies to coal tar-containing creams, lotions, and ointments that are intended to remain on the skin. Soap products covered by the directions in § 358.750(d) (3) are intended to be washed off. Even though a consumer could be exposed to a soap product containing coal tar for an extended period of time while bathing, the coal tar would be highly diluted and the time of exposure would be considerably less than that of products left on the skin. Therefore, the agency does not believe it is necessary to have a warning concerning the use of soap products containing coal tar in or around the rectum or in the genital area or groin because the exposure time and potential for absorption are significantly less for this type of product.

II. Summary of Significant Changes From the Proposed Rule

1. Proposed §§ 358.712 and 358.752, active ingredients and labeling of drug products for the control of cradle cap, respectively, are not included in this final monograph because no additional data to support this use were submitted to the agency. In addition, the definition of cradle cap in proposed § 358.703(b) is not included in the final monograph. Accordingly, proposed § 358.703(c), (d), and (e) have been redesignated as § 358.703(b), (c), and (d), respectively, in this final monograph.

2. The agency has moved the last sentence under the definition for coal tar in proposed § 358.703(a) of the tentative final monograph to the active ingredient sections for coal tar in § 358.710(a)(1), (b)(1), and (c)(1) in this final monograph. This sentence, which provides information on the concentration of coal tar in the final product, is more appropriately conveyed as part of the active ingredient information. This sentence now reads: "When a coal tar solution, derivative, or fraction is used as the source of coal tar, the labeling shall specify the identity and concentration of the coal tar source used and the concentration of the coal tar present in the final product." (See comment 7 above.)

3. The agency is lowering the lower limit for the concentration of pyrithione zinc in § 358.710(a)(2) from 0.95 percent to 0.3 percent in rinse-off products for the control of dandruff. (See comment 11 above.)

4. The other allowable statements proposed in § 358.750(f) have been incorporated into the indications in § 358.750(b) of this final monograph.

5. The warning in proposed § 358.750(c)(1)(ii), "Avoid contact with the eyes—if this happens, rinse thoroughly with water," has been reworded to improve the reading style as follows: "Avoid contact with the eyes. If contact occurs, rinse eyes thoroughly with water." (See comment 13 above.)

III. The Agency's Final Conclusions on OTC Dandruff, Seborrheic Dermatitis, and Psoriasis Drug Products

Based on available evidence, the agency is issuing a final monograph establishing conditions under which OTC dandruff, seborrheic dermatitis, and psoriasis drug products are generally recognized as safe and effective and not misbranded. Specifically, the agency has determined

that the only ingredients that meet monograph conditions are coal tar preparations and salicylic acid for dandruff, seborrheic dermatitis, and soriasis; pyrithione zinc and selenium ulfide for dandruff and seborrheic dermatitis; sulfur for dandruff; and salicylic acid and sulfur in combination for dandruff. All other ingredients and combinations that were considered in this rulemaking have been determined to be nonmonograph conditions for use in an OTC dandruff, seborrheic dermatitis, and psoriasis drug product.

In the Federal Register of November 7, 1990 (55 FR 46914), the agency published a final rule in 21 CFR Part 310 establishing that certain active ingredients that had been under consideration in a number of OTC drug rulemaking proceedings were not generally recognized as safe and effective. That final rule included in § 310.545(a)(7) a number of OTC dandruff, seborrheic dermatitis, and psoriasis active ingredients and was effective on May 7, 1991. This current final rule does not result in the addition of any other ingredients to those already listed in § 310.545(a)(7). However, the parenthetical statement following menthol in the list of ingredients in § 310.545(a)(7), which reads "Does not apply to the use of menthol as an antipruritic when used in combination with the Category I antidandruff gredient coal tar," is now being eleted because the data submission supporting this combination was found to be inadequate. (See comment 14 above.) Accordingly, any drug product labeled, represented, or promoted for use as an OTC dandruff, seborrheic dermatitis, or psoriasis drug product that contains any of the ingredients listed in § 310.545(a)(7) or that is not in conformance with the monograph (21 CFR part 358, subpart H) may be considered a new drug within the meaning of section 201(p) of the act (21 U.S.C. 321(p)) and misbranded under section 502 of the act (21 U.S.C. 352) and may not be marketed for this use unless it is the subject of an approved application under section 505 of the act (21 U.S.C. 355) and part 314 of the regulations (21 CFR part 314). An appropriate citizen petition to amend the monograph may also be submitted under 21 CFR 10.30 in lieu of an application. Any OTC dandruff, seborrheic dermatitis, or psoriasis drug product initially introduced or initially delivered for introduction into interstate commerce after the effective date of the final rule mentioned above or this final le that is not in compliance with the regulations is subject to regulatory action.

As a convenience to the reader, the following list is included as a summary of final agency action on the categorization and uses of dandruff, seborrheic dermatitis, and psoriasis active ingredients considered in this rulemaking.

Active ingredients	Category [1]	Uses [2]
Alkyl isoquinolinium bromide.	NM	A
Allantoin	NM	A
Benzalkonium chloride.	NM	A
Benzethonium chloride.	NM	A
Benzocaine	NM	A
Boric acid	NM	A
Calcium undecylenate.	NM	A
Captan	NM	A
Chloroxylenol	NM	A
Coal tar preparations.	M	A
Colloidal oatmeal	NM	A
Cresol, saponated.	NM	A
Ethohexadiol	NM	A
Eucalyptol	NM	A
Juniper tar	NM	A
Lauryl isoquinolinium bromide.	NM	A
Menthol	NM	A
Mercury oleate	NM	A
Methylbenzethonium chloride.	NM	A
Methyl salicylate	NM	A
Phenol	NM	A
Phenolate sodium.	NM	A
Pine tar	NM	A
Povidone-iodine	NM	A
Pyrithione zinc	M	D, S
Resorcinol	NM	A
Salicylic acid	M	A
Selenium sulfide	M	D, S
Sodium borate	NM	A
Sodium salicylate	NM	A
Sulfur	M	D
Thymol	NM	A
Undecylenic acid	NM	A

[1] NM = Nonmonograph, M = Monograph
[2] D = Dandruff, S = Seborrheic dermatitis, P = Psoriasis, A = All Uses

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (51 FR 27346 at 27362). The agency has examined the economic consequences of this final rule in conjunction with other rules resulting from the OTC drug review. In a notice published in the Federal Register of February 8, 1983 (48 FR 5806), the agency announced the availability of an assessment of these economic impacts. The assessment determined that the combined impacts of all the rules resulting from the OTC drug review do not constitute a major rule according to the criteria established by Executive Order 12291. The agency therefore concludes that no one of these rules, including this final 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 (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 dandruff, seborrheic dermatitis, and psoriasis drug products is not expected to pose such an impact on small businesses. This final rule will require some relabeling for products containing monograph ingredients. Manufacturers will have one year to implement this relabeling. This final rule will also require reformulation of combination products containing coal tar and menthol to delete the menthol. For all other nonmonograph active ingredients listed in the chart above, the effective date was May 7, 1991, after which products containing these ingredients could no longer be initially introduced or initially delivered for introduction into interstate commerce. Therefore, the agency certifies that this final rule will not have a significant economic impact on a substantial number of small entities.

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

List of Subjects

21 CFR Part 310

Administrative practice and procedure, Drugs, Labeling, Medical devices, Reporting and recordkeeping requirements.

21 CFR Part 358

Labeling, Miscellaneous external drug products, Over-the-counter drugs.

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, 21 CFR parts 310 and 358 are amended as follows:

PART 310—NEW DRUGS

1. The authority citation for 21 CFR part 310 continues to read as follows:

Authority: Secs. 201, 301, 501, 502, 503, 505, 506, 507, 512–516, 520, 601(a), 701, 704, 705, 706 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 321, 331, 351, 352, 353, 355, 356, 357, 360b–360f, 360j, 361(a), 371, 374, 375, 376); secs. 215, 301, 302(a), 351, 354–360F of the Public Health Service Act (42 U.S.C. 216, 241, 242(a), 262, 263b–263n).

2. Section 310.545 is amended in paragraph (a)(7) by removing the entry "Methol" including the parenthetical statement and alphabetically adding the entry "Menthol", by revising the introductory text of paragraph (d), and by adding paragraph (d)(3) to read as follows:

§ 310.545 Drug products containing certain active ingredients offered over-the-counter (OTC) for certain uses.

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1), (d)(2), and (d)(3) of this section.

* * * * *

(3) December 4, 1992, for products subject to paragraph (a)(7) of this section that contain menthol as an antipruritic in combination with the antidandruff ingredient coal tar identified in § 358.710(a)(1) of this chapter.

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

3. The authority citation for 21 CFR part 358 continues to read as follows:

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

4. Subpart G is reserved and new subpart H, consisting of §§ 358.701 through 358.750, is added to read as follows:

Subpart G—[Reserved]

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

Sec.

Subpart G—[Reserved]

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 of the conditions in this subpart and each general condition established in § 330.1 of this chapter.

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

§ 358.703 Definitions.

As used in this subpart:

(a) *Coal tar.* 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 1,100 °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.

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

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

(d) *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 of 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. When a coal tar solution, derivative, or fraction is used as the source of the coal tar, the labeling shall specify the identity and concentration of the coal tar source used and the concentration of the coal tar present in the final product.

(2) Pyrithione zinc, 0.3 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. When a coal tar solution, derivative, or fraction is used as the source of the coal tar, the labeling shall specify the identity and concentration of the coal tar source used and the concentration of the coal tar present in the final product.

(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. When a coal tar solution, derivative, or fraction is used as the source of the coal tar, the labeling shall specify the identity and concentration of the coal tar source used and the concentration of the coal tar present in the final product.

(2) Salicylic acid, 1.8 to 3 percent.

§ 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," the phrase listed in paragraph (b)(1) of this section and may contain any of the terms listed in paragraph (b)(2) or (b)(3) of this section. Other truthful and nonmisleading statements, describing only the indications for use that have been established and listed in paragraph (b) of this section, may also be used, as provided in § 330.1(c)(2) of this chapter, subject to the provisions of section 502 of the Federal Food, Drug, and Cosmetic Act (the act) relating to misbranding and the prohibition in section 301(d) of the act against the introduction or delivery for introduction into interstate

commerce of unapproved new drugs in violation of section 505(a) of the act.

(1) ("For 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 or phrases may be used in place of or in addition to the words "For the relief of" or "Controls" in the indications in paragraph (b)(1) 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."

(3) The following terms may be used in place of the words "the symptoms of" in the indications in paragraph (b)(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 contact occurs, rinse eyes 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 regular soap."

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

Dated: July 31, 1991.

David A. Kessler,

Commissioner of Food and Drugs.

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