

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Parts 310 and 358

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DDM

[Docket No. 2005N-0448]

RIN 0910-AF49

Dandruff, Seborrheic Dermatitis, and Psoriasis Drug Products Containing Coal Tar and Menthol for Over-the-Counter Human Use; Amendment to the Monograph

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule amending the final monograph (FM) for over-the-counter (OTC) dandruff, seborrheic dermatitis, and psoriasis drug products to include the combination of 1.8 percent coal tar solution and 1.5 percent menthol in a shampoo drug product to control dandruff. FDA did not receive any comments or data in response to its previously proposed rule to include this combination. This final rule is part of FDA's ongoing review of OTC drug products.

DATES: *Effective Date:* This regulation is effective [*insert date 30 days after date of publication in the Federal Register*].

FOR FURTHER INFORMATION CONTACT: Michael L. Chasey, Center for Drug Evaluation and Research, Food and Drug Administration, 10903 New Hampshire Ave., Bldg. 22, MS 5411, Silver Spring, MD 20993, 301-796-2090.

SUPPLEMENTARY INFORMATION:

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I. Background

In the **Federal Register** of December 4, 1979 (44 FR 69768), FDA published an advance notice of proposed rulemaking (ANPR) to establish a monograph for OTC external analgesic drug products. The ANPR includes the recommendations of the Advisory Review Panel on OTC Topical Analgesic, Antirheumatic, Otic, Burn, and Sunburn Prevention and Treatment Drug Products (the Topical Analgesic Panel). The Topical Analgesic Panel concluded that menthol is safe and effective for use as an OTC external antipruritic (anti-itch) ingredient in concentrations of 1.0 percent or less and as an external counterirritant in concentrations exceeding 1.25 percent up to 16 percent. In the **Federal Register** of February 8, 1983 (48 FR 5852), FDA's proposed monograph, or tentative final monograph (TFM), for OTC external analgesic drug products included menthol as an antipruritic ingredient at concentrations from 0.1 percent to 1.0 percent.

In the **Federal Register** of December 3, 1982 (47 FR 54646), FDA published an ANPR to establish a monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products. The ANPR includes the recommendations of the Advisory Review Panel on OTC Miscellaneous External Drug Products (the Miscellaneous External Panel) concerning OTC drug products for the control of dandruff, seborrheic dermatitis, and psoriasis. The Miscellaneous External Panel recommended coal tar preparations as safe and effective for use as shampoos for controlling dandruff. The Miscellaneous External Panel also concluded that menthol is safe at concentrations of 0.04 to 1.5 percent, but that there were insufficient effectiveness data to include menthol in the monograph for controlling dandruff. The Miscellaneous External Panel further

noted that menthol's activity to temporarily relieve itching should not be considered the same as control of dandruff.

In the **Federal Register** of July 30, 1986 (51 FR 27346), FDA published its TFM for OTC dandruff, seborrheic dermatitis, and psoriasis drug products. No new information was submitted for menthol. Therefore, menthol was not included in the TFM.

In the **Federal Register** of December 4, 1991 (56 FR 63554), FDA issued a FM for OTC dandruff, seborrheic dermatitis, and psoriasis drug products (21 CFR part 358, subpart H). The FM includes a discussion of a study comparing two shampoo formulations for relief of scalp itching associated with dandruff. One formulation contained the combination of 9 percent coal tar solution and 1.5 percent menthol and the other contained coal tar as a single ingredient. FDA determined that the study had a number of major design flaws. For example, the study did not include a group of subjects who only used menthol. Thus, the individual contributions of coal tar and menthol to the effectiveness of the combination product could not be determined from the study. In addition, the statistical analysis of the study results was not valid. FDA concluded that the study did not demonstrate that the combination product offers any advantage over the product containing only coal tar. Thus, FDA concluded that the coal tar-menthol combination is not generally recognized as safe and effective (GRASE) for the control of dandruff based on the study. This combination was placed in a list of active ingredients found not to be GRASE (21 CFR 310.545(d)(3)).

II. Amendment of the Dandruff, Seborrheic Dermatitis, and Psoriasis FM

In 1993, FDA received a petition containing new data in support of the combination of coal tar and menthol for the relief of scalp itching associated

with dandruff. This new study addressed the concerns raised by FDA with the original study in the FM. The new study was a three-arm study, so the effectiveness of the individual ingredients could be properly compared to the combination product. In addition, the appropriate statistics were used to analyze the data. The study shows that both menthol alone as well as the combination of menthol and coal tar provide greater itch relief than coal tar alone at 5, 15, and 30 minutes after shampooing and that the differences at each timepoint were statistically significant. Although menthol alone provides itch relief, FDA has no data to support menthol as a single active ingredient for general relief and control of the non-pruritic symptoms of dandruff (e.g., scaling). Thus, in the **Federal Register** of December 9, 2005 (70 FR 73178), FDA published a proposed rule (PR) to amend the FM for OTC dandruff, seborrheic dermatitis, and psoriasis drug products to include the combination of 1.8 percent coal tar solution and 1.5 percent menthol as GRASE in a shampoo drug product to control dandruff and relieve scalp itching associated with dandruff.

FDA did not receive any comments or data in response to the proposed amendment to the final rule. Therefore, in this final rule, FDA is adding the combination of 1.8 percent coal tar and 1.5 percent menthol to § 358.720 (21 CFR 358.720) and removing the combination from § 310.545(d)(3) (21 CFR 310.545(d)(3)). As proposed, FDA is also adding new § 358.760 (21 CFR 358.760) to describe the labeling for this combination. It reads as follows:

- Statement of identity (§ 358.760(a)(1)): “dandruff/anti-itch shampoo” or “antidandruff/anti-itch shampoo”

- Indication (§ 358.760(b)(1) and (b)(2)): “[bullet] [select one of the following: ‘for relief of’ or ‘controls’] the symptoms of dandruff [bullet] [select one of the following: ‘additional’ or ‘extra’] relief of itching due to dandruff”
- Warnings (§ 358.760(c)(1) and (c)(2)): those listed in § 358.750(c)(1) and (c)(2)
- Directions (§ 358.760(d)(1)): “[bullet] wet hair [bullet] apply shampoo and work into a lather [bullet] rinse thoroughly [bullet] for best results, use at least twice a week or as directed by a doctor”

Any OTC dandruff, seborrheic dermatitis, or psoriasis drug product containing this combination of ingredients that is initially introduced or initially delivered for introduction into interstate commerce after the effective date of this final rule and is not in compliance with the regulations is subject to regulatory action.

FDA is adding the combination of 1.8 percent coal tar and 1.5 percent menthol and corresponding labeling and is also revising § 358.720(a) to correct an error. Section 358.720(a) references “sulfur identified in § 358.710(a)(6),” but the paragraph should reference “sulfur identified in § 358.710(a)(7).” This error was introduced when micronized selenium sulfide was added to the monograph and § 358.710(a) was renumbered (58 FR 17554 and 59 FR 4000).

III. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866, the Regulatory Flexibility Act (5 U.S.C. 601–612), and the Unfunded Mandates Reform Act of 1995 (2 U.S.C. 1501 *et seq.*). Executive Order 12866 directs agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages; distributive impacts; and

equity). Under the Regulatory Flexibility Act, if a rule may have a significant economic impact on a substantial number of small entities, an agency must analyze regulatory options that would minimize any significant impact of the rule on small entities. Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of costs and benefits, before proposing “any rule that includes any Federal mandate that may result in the expenditure by state, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million or more (adjusted annually for inflation) in any one year.”

FDA concludes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. This final rule is not a significant regulatory action as defined by the Executive order and so is not subject to review under the Executive order. As discussed in this section, FDA has determined that this final rule will not have significant economic impact on a substantial number of small entities under the Regulatory Flexibility Act. The Unfunded Mandates Reform Act does not require FDA to prepare a statement of costs and benefits for this final rule because the rule is not expected to result in any 1-year expenditure that would meet or exceed \$100 million adjusted for inflation. The current threshold after adjustment for inflation is about \$118 million, using the most current (2004) Implicit Price Deflator for the Gross Domestic Product.

The purpose of this final rule is to allow an additional combination of active ingredients for OTC antidandruff drug products. Manufacturers can reformulate their OTC antidandruff drug products that contain coal tar to include the combination or can manufacture a new combination product containing coal tar and menthol. Reformulating or manufacturing a new

combination product might result in additional product sales but, in either case, is optional. Thus, this final rule will not impose a significant economic burden on affected entities. Therefore, FDA certifies that this final rule will not have a significant economic impact on a substantial number of small entities. No further analysis is required under the Regulatory Flexibility Act (5 U.S.C. 605(b)).

IV. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements proposed in this document are not subject to review by the Office of Management and Budget because they do not constitute a “collection of information” under the Paperwork Reduction Act of 1995 (44 U.S.C. 3501 *et seq.*). Rather, the labeling statements are a “public disclosure of information originally supplied by the Federal government to the recipient for the purpose of disclosure to the public” (5 CFR 1320.3(c)(2)).

V. Environmental Impact

FDA has determined under 21 CFR 25.31(a) 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.

VI. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule will have a preemptive effect on State law. Section 4(a) of the Executive order requires agencies to “construe * * * a Federal statute to preempt State law only where the statute contains an express preemption provision or there is some other clear evidence that the Congress intended preemption of State law, or where the exercise of State authority conflicts with the exercise of Federal authority

under the Federal statute.” Section 751 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 379r) is an express preemption provision. Section 751(a) of the act (21 U.S.C. 379r(a)) provides that:

* * * no State or political subdivision of a State may establish or continue in effect any requirement—* * * (1) that relates to the regulation of a drug that is not subject to the requirements of section 503(b)(1) or 503(f)(1)(A); and (2) that is different from or in addition to, or that is otherwise not identical with, a requirement under this Act, the Poison Prevention Packaging Act of 1970 (15 U.S.C. 1471 *et seq.*), or the Fair Packaging and Labeling Act (15 U.S.C. 1451 *et seq.*).

Currently, this provision operates to preempt States from imposing requirements related to the regulation of nonprescription drug products. (See Section 751(b) through (e) of the act for the scope of the express preemption provision, the exemption procedures, and the exceptions to the provision.)

This final rule amends the FM for OTC dandruff, seborrheic dermatitis, and psoriasis drug products to include the combination of 1.8 percent coal tar solution and 1.5 percent menthol in a shampoo drug product to control dandruff. Although this final rule has a preemptive effect, in that it precludes States from promulgating requirements related to labeling for OTC dandruff, seborrheic dermatitis, and psoriasis drug products that are different from or in addition to, or not otherwise identical with a requirement in the final rule, this preemptive effect is consistent with what Congress set forth in section 751 of the act. Section 751(a) of the act displaces both State legislative requirements and State common law duties. We also note that even where the express preemption provision is not applicable, implied pre-emption may arise (see *Geier v. American Honda Co.*, 529 US 861 (2000)).

FDA believes that the preemptive effect of the final rule is consistent with Executive Order 13132. Section 4(e) of the Executive order provides that “when an agency proposes to act through adjudication or rulemaking to preempt State law, the agency shall provide all affected State and local officials notice and an opportunity for appropriate participation in the proceedings.”

On January 18, 2007, FDA’s Division of Federal and State Relations provided notice via fax and email transmission to elected officials of State governments and their representatives of national organizations. The notice provided the States with further opportunity for input on the rule. It advised the States of the publication of the December 9, 2005, proposed rule and encouraged State and local governments to review the notice and to provide any comments to the docket (2005N–0448) by a date 30 days from the date of the letter (i.e., by February 20, 2007), or to contact certain named individuals. FDA received no comments in response to this notice. The notice has been filed in the above numbered docket.

List of Subjects

21 CFR Part 310

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

21 CFR Part 358

Labeling, 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: 21 U.S.C. 321, 331, 351, 352, 353, 355, 360b–360f, 360j, 361(a), 371, 374, 375, 379e; 42 U.S.C. 216, 241, 242(a), 262, 263b–263n.

- 2. Section 310.545 is amended by revising paragraph (d)(3) to read as follows:

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

* * * * *

(d) * * *

(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. This section does not apply to products allowed by § 358.720(b) of this chapter after *[insert date 30 days after date of publication in the Federal Register]*.

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: 21 U.S.C. 321, 351, 352, 353, 355, 360, 371.

- 4. Section 358.720 is revised to read as follows:

§ 358.720 Permitted combinations of active ingredients.

(a) *Combination of active ingredients for the control of dandruff.* Salicylic acid identified in § 358.710(a)(4) may be combined with sulfur identified in § 358.710(a)(7) provided each ingredient is present within the established concentration and the product is labeled according to § 358.750.

(b) *Combination of control of dandruff and external analgesic active ingredients.* Coal tar identified in § 358.710(a)(1) may be used at a concentration of 1.8 percent coal tar solution, on a weight to volume basis, in combination with menthol, 1.5 percent, in a shampoo formulation provided the product is labeled according to § 358.760.

■ 5. New § 358.760 is added to read as follows:

§ 358.760 Labeling of permitted combinations of active ingredients for the control of dandruff.

The statement of identity, indications, warnings, and directions for use, respectively, applicable to each ingredient in the product may be combined to eliminate duplicative words or phrases so that the resulting information is clear and understandable.

(a) *Statement of identity.* For a combination drug product that has an established name, the labeling of the product states the established name of the combination drug product, followed by the statement of identity for each ingredient in the combination, as established in the statement of identity sections of the applicable OTC drug monographs.

(1) *Combinations of control of dandruff and external analgesic active ingredients in § 358.720(b).* The label states “dandruff/anti-itch shampoo” or “antidandruff/anti-itch shampoo”.

(2) [Reserved]

(b) *Indications.* The labeling of the product states, under the heading “Uses,” one or more of the phrases listed in this paragraph (b), as appropriate. Other truthful and nonmisleading statements, describing only the uses that have been established and listed in this paragraph (b), 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) *Combinations of control of dandruff and external analgesic active ingredients in § 358.720(b)*. The labeling states “[bullet] [select one of the following: ‘for relief of’ or ‘controls’] the symptoms of dandruff [bullet] [select one of the following: ‘additional’ or ‘extra’] relief of itching due to dandruff”.

(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 indication in paragraph (b)(1) of this section: “scalp” (select one or more of the following: “itching,” “irritation,” “redness,” “flaking,” “scaling”) “associated with”.

(c) *Warnings*. The labeling of the product states, under the heading “Warnings,” the warning(s) listed in § 358.750(c)(1) and (c)(2).

(d) *Directions*. The labeling of the product states, under the heading “Directions,” directions that conform to the directions established for each ingredient in the directions sections of the applicable OTC drug monographs, unless otherwise stated in this paragraph (d). When the time intervals or age limitations for administration of the individual ingredients differ, the directions for the combination product may not contain any dosage that exceeds those established for any individual ingredient in the applicable OTC

drug monograph(s), and may not provide for use by any age group lower than the highest minimum age limit established for any individual ingredient.

(1) *Combinations of control of dandruff and external analgesic active ingredients in § 358.720(b)*. The labeling states “[bullet] wet hair [bullet] apply

shampoo and work into a lather [bullet] rinse thoroughly [bullet] for best results, use at least twice a week or as directed by a doctor”.

(2) [Reserved]

Dated: 2/26/07
February 26, 2007.



Jeffrey Shultz,
Assistant Commissioner for Policy.

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