

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 358

[Docket No. 2002N-0058]

RIN 0910-AA01

Pediculicide Drug Products for Over-the-Counter Human Use; Amendment of Final 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) pediculicide drug products to revise labeling for the statement of identity, warnings, directions, and other required statements. Pediculicide drug products are used for the treatment of head, pubic (crab), and body lice. FDA is issuing this final rule as part of its ongoing review of OTC drug products after considering public comment on its proposed regulation and all relevant data and information that have come to the agency's attention.

DATES: *Effective Date:* This final rule is effective [*insert date 18 months after date of publication in the Federal Register*].

Compliance Dates: The compliance date for OTC pediculicide drug products with annual sales less than \$25,000 is [*insert date 24 months after date of publication in the Federal Register*]. The compliance date for all other OTC pediculicide drug products is [*insert date 18 months after date of publication in the Federal Register*].

FOR FURTHER INFORMATION CONTACT: Michael T. Benson, Center for Drug Evaluation and Research (HFD-560), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-2222.

SUPPLEMENTARY INFORMATION:

I. Background

In the **Federal Register** of December 14, 1993 (58 FR 65452), FDA published a final rule in the form of a FM in part 358 (21 CFR part 358, subpart G) establishing conditions under which OTC pediculicide drug products are generally recognized as safe and effective. The effective date of the final rule was December 14, 1994. Since that time, FDA has determined that labeling in the statement of identity, warnings, directions, and certain other required statements in the pediculicide monograph should be amended.

In the **Federal Register** of March 17, 1999 (64 FR 13254), FDA published a final rule that established a standardized format and standardized content requirements for OTC drug product labeling in § 201.66 (21 CFR 201.66). In that same final rule (64 FR 13254 at 13296), FDA amended the FM for OTC pediculicide drug products and removed the requirement in § 358.650(d)(1) that the direction “Important: Read warnings before using” be printed in all capital letters. The sentence now needs to appear in boldface type with only the word “Important” and the first letter in the word “Read” capitalized.

In the **Federal Register** of May 10, 2002 (67 FR 31739), FDA published a proposed rule to amend the FM for OTC pediculicide drug products to revise labeling for the statement of identity, warnings, directions, and other required statements to increase the probability of treatment success with these products. In response to that proposal, one OTC trade association and a professor of

clinical toxicology submitted comments, which FDA is responding to in this document.

II. The Agency’s Conclusion on the Comments

A. Comments in Agreement with the Proposed Rule

(Comment 1) One comment agreed completely with the proposed recommended label changes. Another comment agreed with the following proposed changes:

- New statement of identity (i.e., remove “pediculicide” and just state “Lice treatment” by itself);
- Simplified indications under the heading “Uses”;
- Formatting changes using subheadings (i.e., “Do not use,” “Ask a doctor before use,” “When using this product,” and “Stop use and ask a doctor if”);
- Bulleted statements under each subheading.

B. Comments with Labeling Recommendations

(Comment 2) One comment contended that the proposed additional directions are too extensive to fit on pediculicide product carton labels. The comment stated that lengthy, detailed directions for environmental control of lice and combing the hair and “other information” would be more appropriately provided in a package insert than on a carton label. The comment agreed that essential treatment directions should be on the outer label, but that consumers do not need to be able to read the entire detailed instructions at the point of purchase. The comment recommended that the outer package have a statement directing consumers to an insert for more complete directions. The comment suggested “See brochure inside for other important information to help get rid of lice.” The comment also added that a statement about use of a comb should be optional on the outer label and

should instruct consumers to see the package insert for complete directions and could incorporate a reference to a comb provided in the package.

FDA considered the length of the additional directions and provided in the May 10, 2002 proposal (§ 358.650(e)) that the detailed information required under the heading “Other information” may appear in a package insert. If that occurs, the “Other information” section on the outer label only needs to include a statement that refers to the package insert for additional information. The information about use of a comb is part of the essential treatment directions (§ 358.650(d)(5)) and, thus, needs to appear on the outer label. If the product does not have a comb with it, consumers would need to know at the point of purchase that they may also need to purchase a special comb to use with the product. FDA is clarifying the introductory paragraph in § 358.650(e) to read that if a package insert is used, the “Other information” section on the outer label shall include a statement referring to the package insert for additional information.

(Comment 3) One comment recommended that the directions proposed in § 358.650(d)(4)(i) or (d)(4)(ii), (d)(6), (d)(7), and (d)(8) appear both on the outer package label and in the package insert. The information includes the following provisions:

- Application directions for shampoo or nonshampoo products,
- Directions for a followup treatment,
- Instructions to see doctor if the infestation continues,
- Instruction to consult a doctor for children under 2 years of age.

FDA agrees with the comment. Directions that appear on the outer package label in accordance with § 201.66(c) may be restated in a package insert.

(Comment 4) One comment disagreed with the agency’s change from 2 weeks to 4 weeks for the time items that cannot be washed should be sealed

in a plastic bag (§ 358.650(e)(1)). The comment stated that FDA gave no rationale for doubling the time and pediculicide manufacturers know of no evidence showing more than 2 weeks is needed to prevent reinfestation.

FDA initiated the change for sealing items that cannot be washed in a plastic bag from 2 to 4 weeks for greater assurance of preventing head lice reinfestation. In the last few years, pediculosis fact sheets have recommended longer sealing times. One sheet (Ref. 1) instructs to “pack the items in a sealed plastic bag for a minimum of two weeks.” Another sheet (Ref. 2) instructs to “pack non-washable items in a sealed plastic bag for 21 days to eliminate the risk from dormant nits.” Based on these recent recommendations, the agency has determined that a 4-week time period will give greater assurance of preventing head lice reinfestation.

(Comment 5) One comment stated that the amended final monograph should allow for special instructions specific to particular products to enhance product-specific directions. The comment gave examples of “shake the product well before use,” “apply to dry hair,” or conditions for storage. The comment requested that the monograph state that “a reasonable degree of flexibility will be given to companies choosing to amplify the directions appropriately.”

The agency disagrees with the need to include the comment’s suggested statements in the FM for OTC pediculicide drug products. That monograph does not prohibit manufacturers from including statements such as “shake well before using” or information about conditions for storage in the product’s labeling. The direction under the heading “Treat” for shampoo and nonshampoo products in § 358.650(d)(4)(i) and (d)(4)(ii) imply that the hair is dry before the product is first applied. FDA is amending these sections to give the option of adding the word “dry” before “hair”.

C. Will Labeling for New Drug Application (NDA) Products be Revised at the Same Time as the Monograph Products?

(Comment 6) One comment asked FDA to coordinate the revised NDA labeling for OTC pediculicide drug products marketed under NDAs and under the OTC drug monograph. The comment stated that the implementation for all products should occur at the same time.

FDA strives for consistency in labeling of similar products that are marketed OTC under an OTC drug monograph or an NDA. The effective date for the amended labeling in this final rule is 18 months after the date of publication in the **Federal Register**. The agency intends to notify NDA holders to make changes in labeling consistent with this final rule and believes these changes can be completed by the effective date.

III. The Agency's Final Conclusions

A. Summary of Major Labeling Changes

Based on the available evidence, FDA is issuing a final rule amending the FM for OTC pediculicide drug products to make the following changes:

- *Statement of Identity.* We revised the “*Statement of identity*” to read “lice treatment” and eliminated the term “pediculicide.”

- *Warnings.*

(1) We shortened some warnings and stated all warnings in the new format in § 201.66 using the subheadings “Do not use”, “Ask a doctor before use if you are”, “When using this product”, and “Stop use and ask a doctor if”.

(2) We revised one warning for greater clarity by adding a few words after the statement “See a doctor” to read “Do not use • near eyes • inside nose, mouth, or vagina • on lice in eyebrows or eyelashes. See a doctor if lice are present in these areas.”

- *Directions.* We added the following:

(1) Two introductory statements entitled “Important: Read warnings before use” [statement shall appear first and in bold type] and “adults and children 2 years and over” [in bold type];

(2) Headings entitled “Inspect”, “Treat”, and “Remove lice and their eggs (nits)”;

(3) “Dry” as an optional word before “hair” in the first sentence in the heading for “Treat” for shampoo and nonshampoo products.

- *Other information.*

(1) We allow information to appear in a package insert.

(2) We expanded the time for sealing items in a plastic bag from 2 to 4 weeks.

(3) We added the statement “ • vacuum all carpets, mattresses, upholstered furniture, and car seats that may have been used by affected people”.

B. Statement About Warnings

Mandating warnings in an OTC drug monograph does not require a finding that any or all of the OTC drug products covered by the monograph actually caused an adverse event, and FDA does not so find. Nor does FDA’s requirement of warnings repudiate the prior OTC drug monographs and monograph rulemakings under which the affected drug products have been lawfully marketed. Rather, as a consumer protection agency, FDA has determined that warnings are necessary to ensure that these OTC drug products continue to be safe and effective for their labeled indications under ordinary conditions of use as those terms are defined in the Federal Food, Drug, and Cosmetic Act. This judgment balances the benefits of these drug products against their potential risks (see 21 CFR 330.10(a)).

FDA's decision to act in this instance need not meet the standard of proof required to prevail in a private tort action (*Glastetter v. Novartis Pharmaceuticals Corp.*, 252 F.3d 986, 991 (8th Cir. 2001)). To mandate warnings, or take similar regulatory action, FDA need not show, nor do we allege, actual causation. For an expanded discussion of case law supporting FDA's authority to require such warnings, see Labeling of Diphenhydramine-Containing Drug Products for Over-the-Counter Human Use final rule (67 FR 72555, December 6, 2002).

C. Marketing Conditions

No OTC pediculicide drug product that is marketed under part 358, subpart G, and that contains a nonmonograph condition may be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved NDA:

- 24 months after the date of publication of this final rule in the **Federal Register**] for products with sales less than \$25,000;
- 18 months after the date of publication in the **Federal Register** for all other such drug products.

Further, any OTC drug product subject to this final rule that is repackaged or relabeled after the compliance dates in the final rule must be in compliance with part 358, subpart G regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily as soon as possible.

IV. Analysis of Impacts

FDA has examined the impacts of the final rule under Executive Order 12866 and 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 has a significant 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 of anticipated costs and benefits before proposing any rule that may result in an expenditure in any 1 year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

FDA concludes that this final rule is consistent with the principles set out in Executive Order 12866 and in these two statutes. The 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 a significant economic impact on a substantial number of small entities. The Unfunded Mandates Reform Act of 1995 does not require FDA to prepare a statement of costs and benefits for this final rule, because the final rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation. The current inflation adjusted statutory threshold is about \$110 million.

The purpose of this final rule is to revise and improve the statement of identity, warnings, directions, and other required labeling statements for OTC pediculicide drug products. The revised labeling provides more detailed

information on the proper use of the product and should improve consumers' self-use.

The final rule requires relabeling of OTC pediculicide drug products containing pyrethrum extract with piperonyl butoxide. FDA's drug listing system identifies about 23 manufacturers and 36 marketers of approximately 75 stockkeeping units (SKU) (individual products, packages, and sizes) of OTC pediculicide drug products. There may be a few additional marketers and products that are not identified in the sources FDA reviewed.

FDA does not believe that manufacturers would need to increase the package size to add the additional labeling information. Almost all of these products are marketed in an outer carton which should have adequate space for the additional information. In addition, manufacturers may include the "Other information" section of the labeling in a package insert, which generally has a nominal cost. Assuming that there are about 75 affected OTC SKUs in the marketplace, FDA estimates (based on information provided by OTC drug manufacturers) that the rule would impose total one-time compliance costs on industry for relabeling of about \$3,000 to \$4,000 per SKU, for a total cost of \$225,000 to \$300,000.

FDA believes the actual cost could be lower for several reasons. First, most of the labeling changes will be made by private label small manufacturers that tend to use simpler and less expensive labeling.

Second, FDA is providing a period of 18 months (24 months for products with annual sales less than \$25,000) for manufacturers to implement the new labeling. Thus, manufacturers should be able to use up existing labeling stocks and to make the labeling changes in the normal course of business. Further, manufacturers will not incur any expenses determining how to state the

product's labeling because the final rule provides that information. The final rule does not require any new reporting and recordkeeping activities.

Therefore, no additional professional skills are needed.

FDA considered but rejected several labeling alternatives: (1) A shorter or longer implementation period, and (2) an exemption from coverage for small entities. While the agency believes that consumers would benefit from having this new labeling in place as soon as possible, the agency also acknowledges that a shorter implementation period could significantly increase the compliance costs and these costs could be passed through to consumers. A longer time period would unnecessarily delay the benefit of new labeling to consumers who self-medicate with these drug products. The agency rejects an exemption for small entities because the new labeling information is also needed by consumers who purchase products marketed by those entities. However, a longer compliance date (24 months) is being provided for products with annual sales less than \$25,000.

OTC pediculicide drug products are not the sole products produced by manufacturers affected by this final rule. FDA believes that the incremental costs of this final rule will be less than 1 percent of any of the manufacturer's total sales. 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)).

V. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements 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 statement of identity, warnings, directions, and other information 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)).

VI. 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.

VII. Federalism

FDA has analyzed this final rule in accordance with the principles set forth in Executive Order 13132. FDA has determined that the rule does not contain policies that have substantial direct effects on the States, on the relationship between the National Government and the States, or on the distribution of power and responsibilities among the various levels of government. Accordingly, the agency concludes that the rule does not contain policies that have federalism implications as defined in the Executive order and, consequently, a federalism summary impact statement is not required.

VIII. References

The following references are on display in the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, rm. 1061, Rockville, MD 20852, and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday. (FDA has verified the Web site addresses, but FDA is not responsible for any subsequent changes to the Web site after this document publishes in the **Federal Register**.)

1. Fact sheet from Mason County, Washington State Government Services, “Head Lice (Pediculosis),” <http://www.co.mason.wa.us/health/Headlice.shtml>.

2. Fact sheet from King County, Washington State Government Services, “Communicable Disease Fact Sheet Head Lice (Pediculosis),” <http://www.metrokc.gov/health/prevcont/headlice.htm>.

List of Subjects in 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 part 358 is amended as follows:

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

■ 1. 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.

■ 2. Section 358.650 is revised to read as follows:

§ 358.650 Labeling of pediculicide drug products.

(a) *Statement of identity.* The labeling of the product contains the established name of the drug, if any, and identifies the product as a “lice treatment.”

(b) *Indications.* The labeling of the product states, under the heading “Uses,” the following: “treats head, pubic (crab), and body lice.” 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.

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

(1) “For external use only” in accord with § 201.66(c)(5)(i) of this chapter.

(2) “Do not use [bullet]¹ near eyes [bullet] inside nose, mouth, or vagina [bullet] on lice in eyebrows or eyelashes. See a doctor if lice are present in these areas.”

(3) “Ask a doctor before use if you are [bullet] allergic to ragweed. May cause breathing difficulty or an asthmatic attack.”

(4) “When using this product [bullet] keep eyes tightly closed and protect eyes with a washcloth or towel [bullet] if product gets in eyes, flush with water right away [bullet] scalp itching or redness may occur”.

(5) “Stop use and ask a doctor if [bullet] breathing difficulty occurs [bullet] eye irritation occurs [bullet] skin or scalp irritation continues or infection occurs”.

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

(1) The labeling states “[bullet] Important: Read warnings before use” [statement shall appear first and in bold type].

(2) The labeling states “adults and children 2 years and over:” [in bold type].

(3) For head lice treatment products “Inspect [in bold type] [bullet] check each household member with a magnifying glass in bright light for lice/nits (eggs) [bullet] look for tiny nits near scalp, beginning at back of neck and behind ears [bullet] examine small sections of hair at a time [bullet] unlike

¹ See § 201.66(b)(4) of this chapter for definition of bullet symbol.

dandruff which moves when touched, nits stick to the hair [bullet] if either lice or nits are found, treat with this product”.

(4) Select one of the following:

(i) *For shampoo products* “Treat [in bold type] [bullet] apply thoroughly to (optional, may add “dry”) hair or other affected area. For head lice, first apply behind ears and to back of neck. [bullet] allow product to remain for 10 minutes, but no longer [bullet] use warm water to form a lather, shampoo, then thoroughly rinse [bullet] for head lice, towel dry hair and comb out tangles”.

(ii) *For nonshampoo products* “Treat [in bold type] [bullet] apply thoroughly to (optional, may add “dry”) hair or other affected area. For head lice, first apply behind ears and to back of neck. [bullet] allow product to remain for 10 minutes, but no longer [bullet] wash area thoroughly with warm water and soap or shampoo [bullet] for head lice, towel dry hair and comb out tangles”.

(5) “Remove lice and their eggs (nits) [in bold type] [bullet] use a fine-tooth or special lice/nit comb. Remove any remaining nits by hand (using a throw-away glove). [bullet] hair should remain slightly damp while removing nits [bullet] if hair dries during combing, dampen slightly with water [bullet] for head lice, part hair into sections. Do one section at a time starting on top of head. Longer hair may take 1 to 2 hours. [bullet] lift a 1- to 2-inch wide strand of hair. Place comb as close to scalp as possible and comb with a firm, even motion away from scalp. [bullet] pin back each strand of hair after combing [bullet] clean comb often. Wipe nits away with tissue and discard in a plastic bag. Seal bag and discard to prevent lice from coming back. [bullet]

after combing, thoroughly recheck for lice/nits. Repeat combing if necessary.
[bullet] check daily for any lice/nits that you missed”.

(6) The labeling states “[bullet] a second treatment must be done in 7 to 10 days to kill any newly hatched lice”.

(7) The labeling states “[bullet] if infestation continues, see a doctor for othertreatments”.

(8) The labeling states “children under 2 years:” [in bold type] “ask a doctor”.

(e) *Other information.* The labeling of the product contains the following statements, as appropriate, under the heading “Other information.” This information may appear in a package insert. If a package insert is used, the “Other information” section on the outer carton or container label shall include a statement referring to the package insert for additional information.

(1) “Head lice [highlighted in bold type] [bullet] lay small white eggs (nits) on hair shaft close to scalp [bullet] nits are most easily found on back of neck or behind ears [bullet] disinfect hats, hair ribbons, scarves, coats, towels, and bed linens by machine washing in hot water (above 54 °C (130 °F)), then using hottest dryer cycle for at least 20 minutes [bullet] items that cannot be washed (bedspreads, blankets, pillows, stuffed toys, etc.) should be dry-cleaned or sealed in a plastic bag for 4 weeks, then removed outdoors and shaken out very hard before using again [bullet] items that cannot be washed, dry-cleaned, or stored may be sprayed with a product designed for this purpose [bullet] soak all combs and brushes in hot water (above 54 °C (130 °F)) for at least 10 minutes [bullet] vacuum all carpets, mattresses, upholstered furniture, and car seats that may have been used by affected people”.

(2) “Pubic (crab) lice [highlighted in bold type] [bullet] may be transmitted by sexual contact. Sexual partners should be treated simultaneously to avoid reinfestation [bullet] lice are very small and look like brown or grey dots on skin [bullet] usually cause intense itching and lay small white eggs (nits) on the hair shaft generally close to the skin surface [bullet] may be present on the short hairs of groin, thighs, trunk, and underarms, and occasionally on the beard and mustache [bullet] disinfect underwear by machine washing in hot water (above 54 °C (130 °F)), then using hottest dryer cycle for at least 20 minutes”.

(3) “Body lice [highlighted in bold type] [bullet] body lice and their eggs (nits) are generally found in the seams of clothing particularly in waistline and armpit area [bullet] body lice feed on skin then return to clothing to lay their eggs [bullet] disinfect clothing by machine washing in hot water (above 54 °C (130 °F)), then using hottest dryer cycle for at least 20 minutes [bullet] do not seal clothing in a plastic bag because nits can remain dormant for up to 30 days”.

Dated: December 18, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

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