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DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

21 CFR Parts 201 and 341

[Docket No. 76N-052T]

RIN 0910-AA01

Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the-Counter Human Use; Amendment of Final Monograph for OTC Antitussive Drug Products

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 for over-the-counter (OTC) antitussive drug products (products that relieve cough). Use of topical/inhalant products containing camphor or menthol near a flame, in hot water, or in a microwave oven may cause the products to splatter and cause serious burns to the user. As part of its ongoing review of OTC drug products, FDA is adding warnings and directions to inform consumers about these improper uses and is amending its final regulations for OTC drug labeling requirements to add this new flammability warning for antitussive drug products containing camphor or menthol.

DATES: This rule is effective May 16, 2002. The compliance date for products with annual sales less than \$25,000 is May 16, 2003. The compliance date for all other OTC drug products is May 16, 2002.

FOR FURTHER INFORMATION CONTACT: Elizabeth A. Ryland or Gerald M. Rachanow, 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 August 12, 1987 (52 FR 30042), the agency published the final monograph for OTC antitussive drug products. The monograph included the ingredients camphor and menthol as single topical antitussives in an ointment vehicle or for steam inhalation use. Products containing camphor and menthol in combination are being considered as part of the ongoing rulemaking for OTC cough-cold combination drug products.

When the final monograph was published in 1987, the agency was not aware of safety problems occurring when products that contain camphor or menthol are added to hot water or used in a microwave oven. In the **Federal Register** of July 20, 1998 (63 FR 38762), the agency discussed new information concerning 34 fire-related events (flashing occurred) resulting from antitussive drug products containing camphor and menthol (in an ointment vehicle or an alcohol-based solution) that were placed in hot water or heated in a microwave oven. As a result, the agency proposed a flammability signal word and new warning and direction statements for these products (63 FR 38762 at 38765).

The agency proposed a flammability signal word and a warning (“Keep away from fire or flame”) for any product containing camphor or menthol in an ointment vehicle or for steam inhalation use. The agency also proposed a number of “do not use” warnings (e.g., near an open flame and in a microwave oven) and the following statements in the directions: “See important warnings about not using near a flame, in hot water, or in a microwave oven. Improper use may cause the mixture to splatter and cause burns.”

In response to the proposal, the agency received two comments, copies of which are on public display in the Dockets Management Branch (HFA-305), 5630 Fishers Lane, rm. 1061, Rockville, MD 20852. The agency's responses to the comments follow.

II. The Agency's Conclusions on the Comments

(Comment 1) One comment agreed with the proposal to require additional information to help increase appropriate use of the topical/inhalant drug products containing camphor and menthol.

(Comment 2) Two comments requested that the regulation clarify that a flammability signal word is not required on all products. The comments pointed out that the flammability signal words in 16 CFR 1500.3(b)(10) and (c)(6) state that "flammable" is any substance having a flashpoint above 20 °F and below 100 °F and that no flammability signal word is required if the flashpoint of the substance is above 150 °F. The comments added that camphor and menthol in ointment/cream products have flashpoints over 150 °F and would not need the flammability signal word or warnings, while steam inhalation products in an alcohol vehicle have a flashpoint between 20 °F and below 100 °F and would be labeled as flammable and contain the two proposed flammability warnings. One comment provided the results of flashpoint testing for its ointment, cream, and steam inhalation products (Ref. 1).

The agency has reviewed the testing results and concurs that products with a flashpoint above 150 °F would not need the flammability signal word or warnings. The agency only intended that those products that meet the criteria in 16 CFR 1500.3(b)(10) (flashpoint of 150 °F or below) be labeled with the flammability signal word and warnings. Accordingly, the agency is revising § 341.74(c)(5)(iii) (21 CFR 341.74(c)(5)(iii)) to require that the labeling contains the appropriate flammability signal word and the statement "Keep away from fire or flame" if the product meets the definition of one of the signal words ("extremely flammable," "flammable," "combustible") as described in 16 CFR 1500.3(b)(10). The agency is also amending § 201.66(c)(5)(ii)(C) (21 CFR 201.66(c)(5)(ii)(C)) to include § 341.74(c)(5)(iii) as an example where a flammability warning is found in an OTC drug monograph.

(Comment 3) Two comments requested that the warnings about not using these products in certain ways be included in the “Directions,” and not the “Warnings,” section. The comments contended that the warnings relate to appropriate use of the product and belong in the directions so consumers know how to use the product correctly. The comments argued that because space limitations on small package sizes make it very difficult to fit similar information in two places (warnings and directions), the information should be consolidated in the “Directions” section.

The agency has determined that this information is more appropriate in the “Warnings” section of the labeling. Under the new OTC drug product labeling format in § 201.66(c)(5)(vi), which was issued after the proposal in the current rulemaking, the subheading “When using this product” is used to describe activities consumers should avoid while using the product. Information about not using the product near a flame or in a microwave oven belongs under this subheading. However, because of the importance of the warning information, the agency is including a short cross-reference in the “Directions” section to the location of the information in the “Warnings” section. This approach is consistent with the “choking” warning for water-soluble gums in 21 CFR 201.319 where the information about choking appears in the “Warnings” section and a cross-reference to the warning appears in the “Directions” section.

The agency proposed a two-sentence cross-reference in the “Directions” section that was repetitive of some of the information in the “Warnings” section. The agency is removing the repetitive information in the first proposed sentence (i.e., about not using near a flame, in hot water, or in a microwave oven) and shortening the sentence to refer users to the same information in the “Warnings” section. The revised directions statement now reads: “[bullet] see important warnings under ‘When using this product’ ” [appears as the first statement under the heading “Directions” and is highlighted in bold type]. The agency is moving the second proposed statement about the mixture splattering and causing burns to the “Warnings” section to follow the information about not using near a flame or in a microwave oven, because the second sentence should immediately follow that information.

(Comment 4) Two comments requested that the directions provide different instructions for ointment and steam inhalation products. One comment suggested the following wording for ointment products: “Do not expose to any heat source (including stove or microwave) or place in any container in which you are heating water. Improper use may cause the mixture to splatter and cause burns.” The comment added that steam inhalation products would also include the word “flame” after “stove” and the words “except when adding to cold water in a hot steam vaporizer” after the words “heating water.”

The second comment proposed similar but revised wording for ointment products: “Do not heat. Never expose to flame, microwave, or place in any container in which you are heating water. Improper use may cause the mixture to splatter and cause burns.” The comment added that steam inhalation products should also include the words “except when adding to cold water in a hot steam vaporizer” after the words “heating water.”

As discussed in part II, comment 3 of this document, this information about not using the products in certain ways will appear in the “Warnings” section. The agency agrees that ointment, cream, and steam inhalation products could have slightly different warnings depending on the flashpoint of the products. The data provided by one comment (Ref. 1) showed that the flashpoints of an ointment product were 158 and 165 °F, while the flashpoint of a cream product was 152 °F. As discussed in part II, comment 2 of this document, other manufacturers’ products might have a flashpoint of 150 °F or below and thus be required to have a flammability signal word and warnings. The agency agrees with deletion of the word “flame” from the warnings for ointment/cream products if they are not flammable or combustible. The agency also agrees with inclusion of the words “except when adding to cold water only in a hot steam vaporizer” for steam inhalation products. To increase the amount of information provided to consumers and to state the information in a clear and concise way, the agency is revising the warnings as follows:

- *For any product containing camphor or menthol in a suitable ointment vehicle and that does not contain a flammability signal word as described in 16 CFR 1500.3(b)(10). “When using*

this product, do not • heat • microwave • add to hot water or any container where heating water. May cause splattering and result in burns.” [Information highlighted in bold type.]

• *For any product containing camphor or menthol in a suitable ointment vehicle and that contains a flammability signal word as described in 16 CFR 1500.3(b)(10).* “When using this product, do not • heat • microwave • use near an open flame • add to hot water or any container where heating water. May cause splattering and result in burns.” [Information highlighted in bold type.]

• *For any product containing camphor or menthol for steam inhalation use.* “When using this product, do not • heat • microwave • use near an open flame • add to hot water or any container where heating water except when adding to cold water only in a hot steam vaporizer. May cause splattering and result in burns.” [Information highlighted in bold type.]

There are two types of products containing camphor or menthol for steam inhalation use on the market. One is formulated to be added directly to cold water inside a hot steam vaporizer before the water is heated, and the other is formulated to be placed into the medication chamber of the vaporizer. The agency is modifying the directions in § 341.74(d)(2)(iv) and (d)(2)(v) for products containing camphor or menthol for steam inhalation use to include appropriate directions for both types of these products, as follows:

- *For products formulated to be added directly to cold water inside a hot steam vaporizer.*
- use 1 tablespoonful of solution for each quart of water or 1½ teaspoonsful of solution for each pint of water • add solution directly to cold water only in a hot steam vaporizer • follow manufacturer’s directions for using vaporizer.
- *For products formulated to be placed in the medication chamber of a hot steam vaporizer.*
- place water in the vaporizer and follow manufacturer’s directions for using vaporizer • place solution in the medication chamber only.

(Comment 5) One comment stated that the proposed warning about not using an ointment product in a hot steam vaporizer is inappropriate (because these products are not used in that manner) and will lead to consumer confusion.

The agency notes that 1 of the 21 fire-related events discussed in the proposal (63 FR 38762) involved an ointment product that was added to hot water in a vaporizer. The agency believes that it is important to inform consumers about this potential problem. The portion of the warning about not adding the product to “hot water” covers both hot water in a container on the stove and hot water in a vaporizer; thus, this information should adequately inform consumers and should not cause confusion.

III. Reference

The following reference is on display in the Dockets Management Branch (address above) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. Comment No. C200, Docket No. 76N-052T, Dockets Management Branch.

IV. The Agency's Final Conclusions

The agency concludes that the case reports raise safety concerns that could be alleviated by providing consumers with additional warnings and directions for topical/inhalant OTC antitussive drug products that contain camphor or menthol. Products that meet the definition of one of the signal words (“extremely flammable,” “flammable,” “combustible”) in 16 CFR 1500.3(b)(10) must state the signal word and “Keep away from fire or flame” in their labeling. Consumers need to be informed via warnings not to heat or microwave these products, not to add them to hot water, not to put them in any container where water is being heated (except for adding a steam inhalation product to cold water only in a hot steam vaporizer), and not to use near an open flame (if the product bears a flammability signal word). The agency has included warnings and directions with minor differences to fit the variety of products that might exist and a short cross-reference to the warnings information in the directions section. The agency has revised

proposed warnings and directions in this final rule to state them in the new OTC drug labeling format required by § 201.66.

V. Analysis of Impacts

FDA has examined the impacts of this 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 has 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 requires that agencies prepare a written statement and economic analysis before proposing any rule that may result in an expenditure in any one year by State, local, and tribal governments, in the aggregate, or by the private sector, of \$100 million (adjusted annually for inflation).

The agency believes that this final rule is consistent with the regulatory philosophy and principles identified in the Executive Order. In addition, 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.

The purpose of this final rule is to revise and improve the labeling (add additional warning and direction statements) for safer use of topical/inhalant products that contain camphor, menthol, or both ingredients. This revised labeling addresses the flammability of these products and alerts consumers not to heat or microwave the products, nor to use near an open flame, add to hot water, or put in any container in which water is being heated (with an exception for adding a steam inhalation product to cold water only in a hot steam vaporizer). Potential benefits include

a reduction in the number of flash fires and serious burns that may occur if consumers should misuse these products.

This final rule will require relabeling of topical/inhalant products that contain camphor, menthol, or both ingredients. The agency's Drug Listing System identifies about 30 manufacturers and 80 marketers of over 100 stockkeeping units (SKU's) (individual products, packages, and sizes) of topical/inhalant antitussive drug products containing camphor, menthol, or both ingredients. There may be a few additional marketers and products that are not identified in the sources FDA reviewed.

The agency indicated in the proposal that relabeling costs of the type required by this final rule generally average about \$2,000 to \$3,000 per SKU. In determining this cost, the agency did 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. Assuming that there are about 110 affected OTC SKU's in the marketplace, FDA estimated that the rule would impose total one-time compliance costs on industry for relabeling of about \$220,000 to \$330,000. The agency did not receive any comments on these estimates.

The agency believes the actual cost could be lower for several reasons. First, most of the label changes will be made by private label small manufacturers that tend to use simpler and less expensive labeling. However, the final rule will not require any new reporting and recordkeeping activities. Therefore, no additional professional skills are needed. Second, the agency has made the compliance dates for this final rule the same as the dates for these monographed products to be in compliance with the new standardized format and standardized content requirements for the labeling of OTC drug products (§ 201.66), which are now May 16, 2002 (and May 16, 2003, for products with annual sales less than \$25,000). Manufacturers will not incur any expenses determining how to state the product's labeling. All manufacturers should have ample time to use

up existing labeling stocks and the relabeling costs would be mitigated. Thus, all required labeling changes can be made at the same time, thereby reducing the labeling cost of this final rule.

The agency 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 coordination of this labeling change with implementation of the new OTC "Drug Facts" labeling may significantly reduce the costs of this final rule. Both a shorter and a longer time period for this rule may cost more if firms would have to undertake two successive labeling revisions. In addition, a longer time period would unnecessarily delay the benefit of the new labeling to consumers who self-medicate with these products. The agency rejected an exemption for small entities because the new labeling information is also needed by consumers who purchase products marketed by those entities.

The agency does not believe that this final rule will have a significant economic impact on small entities, using the U.S. Small Business Administration designations for this industry (750 employees). The agency believes that any other unidentified manufacturer of these products is also a small entity. From information available to the agency, it appears that only one small entity manufactures more than three SKU's of these products. Based on the limited number of SKU's each manufacturer has to relabel, the cost for each manufacturer except one should be minimal.

Under the Unfunded Mandates Reform Act, FDA is not required to prepare a statement of costs and benefits for this final rule because this rule is not expected to result in any 1-year expenditure that would exceed \$100 million adjusted for inflation.

This analysis shows that the agency has considered the burden to small entities. Thus, this economic analysis, together with other relevant sections of this document, serves as the agency's final regulatory flexibility analysis, as required under the Regulatory Flexibility Act.

VI. Paperwork Reduction Act of 1995

FDA concludes that the labeling requirements in this final rule 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 requirements 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)).

VII. Environmental Impact

The agency 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.

List of Subjects

21 CFR Part 201

Drugs, Labeling, Reporting and recordkeeping requirements.

21 CFR Part 341

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 201 and 341 are amended as follows:

PART 201—LABELING

1. The authority citation for 21 CFR part 201 continues to read as follows:

Authority: 21 U.S.C. 321, 331, 351, 352, 353, 355, 358, 360, 360b, 360gg–360ss, 371, 374, 379e; 42 U.S.C. 216, 241, 262, 264.

2. Section 201.66 is amended by revising paragraph (c)(5)(ii)(C) to read as follows:

§ 201.66 Format and content requirements for over-the-counter (OTC) drug product labeling.

* * * * *

(c) * * *

(5) * * *

(ii) * * *

(C) Flammability warning, with appropriate flammability signal word(s) (e.g., §§ 341.74(c)(5)(iii), 358.150(c), and 358.550(c) of this chapter). This warning shall follow a subheading containing the appropriate flammability signal word(s) described in an applicable OTC drug monograph or approved drug application.

PART 341—COLD, COUGH, ALLERGY, BRONCHODILATOR, AND ANTI-ASTHMATIC DRUG PRODUCTS FOR OVER-THE-COUNTER HUMAN USE

3. The authority citation for 21 CFR part 341 continues to read as follows:

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

4. Section 341.74 is amended by adding new paragraphs (c)(5)(iii) through (c)(5)(vii), and by revising paragraphs (d)(2)(i), (d)(2)(ii), (d)(2)(iv), and (d)(2)(v) to read as follows:

§ 341.74 Labeling of antitussive drug products.

* * * * *

(c) * * *

(5) * * *

(iii) *For any product containing camphor or menthol in a suitable ointment vehicle or for steam inhalation use and meets the definition of one of the signal words (“extremely flammable,” “flammable,” “combustible”) as described in 16 CFR 1500.3(b)(10). The labeling contains the appropriate flammability signal word(s) followed by a colon and the statement “Keep away from fire or flame.”*

(iv) *For any product containing camphor or menthol in a suitable ointment vehicle and that does not contain a flammability signal word as described in 16 CFR 1500.3(b)(10).* “When using this product, do not [bullet]¹ heat [bullet] microwave [bullet] add to hot water or any container where heating water. May cause splattering and result in burns.” [Information highlighted in bold type.]

(v) *For any product containing camphor or menthol in a suitable ointment vehicle and that contains a flammability signal word as described in 16 CFR 1500.3(b)(10).* “When using this product, do not [bullet] heat [bullet] microwave [bullet] use near an open flame [bullet] add to hot water or any container where heating water. May cause splattering and result in burns.” [Information highlighted in bold type.]

(vi) *For any product containing camphor or menthol for steam inhalation use.* “When using this product, do not [bullet] heat [bullet] microwave [bullet] use near an open flame [bullet] add to hot water or any container where heating water except when adding to cold water only in a hot steam vaporizer. May cause splattering and result in burns.” [Information highlighted in bold type.]

(vii) *For any product formulated in a volatile vehicle.* The labeling contains the following statement under the heading “Other information”: “Close container tightly and store at room temperature away from heat.”

(d) * * *

(2) * * *

(i) *For products containing camphor identified in § 341.14(b)(1) in a suitable ointment vehicle.* The product contains 4.7 to 5.3 percent camphor. “[bullet] see important warnings under ‘When using this product’ ” [appears as the first statement under the heading “Directions” and is highlighted in bold type] [bullet] adults and children 2 years and older: [bullet] rub on the throat and chest in a thick layer [bullet] cover with a warm, dry cloth if desired [bullet] clothing should

¹ For a definition of the term “bullet,” see § 201.66(b)(4) of this chapter.

be loose about throat and chest to help vapors reach the nose and mouth [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

(ii) *For products containing menthol identified in § 341.14(b)(2) in a suitable ointment vehicle.*

The product contains 2.6 to 2.8 percent menthol. “[bullet] see important warnings under ‘When using this product’ ” [appears as the first statement under the heading “Directions” and is highlighted in bold type] [bullet] adults and children 2 years and older: [bullet] rub on the throat and chest in a thick layer [bullet] cover with a warm, dry cloth if desired [bullet] clothing should be loose about throat and chest to help vapors reach the nose and mouth [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

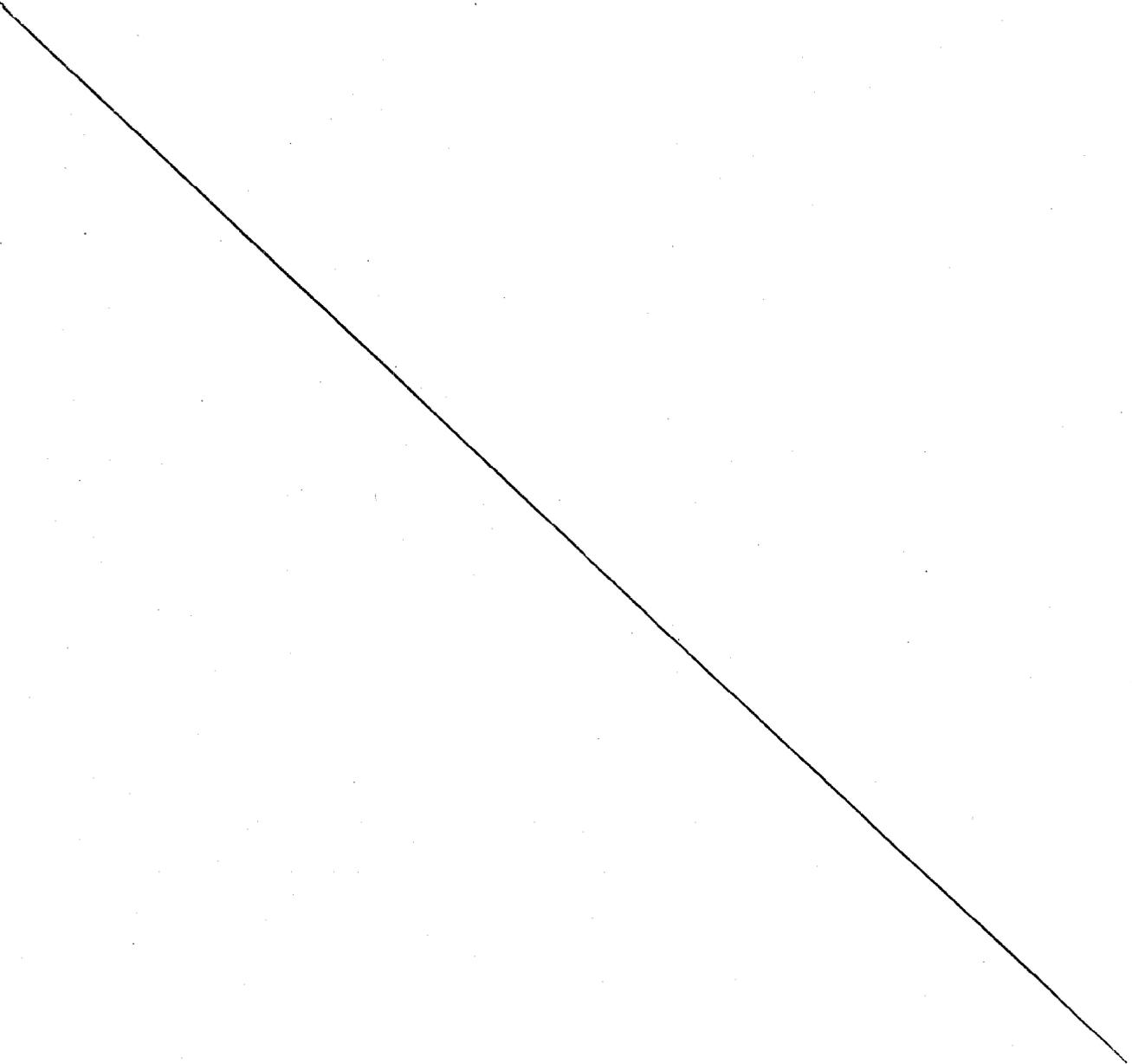
* * * * *

(iv) *For products containing camphor identified in § 341.14(b)(1) for steam inhalation use.*

The product contains 6.2 percent camphor. “[bullet] see important warnings under ‘When using this product’ ” [appears as the first statement under the heading “Directions” and is highlighted in bold type] [bullet] adults and children 2 years and older: (select one of the following, as appropriate: *For products formulated to be added directly to cold water inside a hot steam vaporizer.* [bullet] use 1 tablespoonful of solution for each quart of water or 1½ teaspoonsful of solution for each pint of water [bullet] add solution directly to cold water only in a hot steam vaporizer [bullet] follow manufacturer’s directions for using vaporizer or *For products formulated to be placed in the medication chamber of a hot steam vaporizer.* [bullet] place water in the vaporizer and follow manufacturer’s directions for using vaporizer [bullet] place solution in the medication chamber only) [bullet] breathe in the medicated vapors [bullet] use up to three times daily or as directed by a doctor [bullet] children under 2 years of age: Ask a doctor.

(v) *For products containing menthol identified in § 341.14(b)(2) for steam inhalation use.* The product contains 3.2 percent menthol. “[bullet] see important warnings under ‘When using this product’ ” [appears as the first statement under the heading “Directions” and is highlighted in bold type] [bullet] adults and children 2 years and older: (select one of the following, as appropriate:

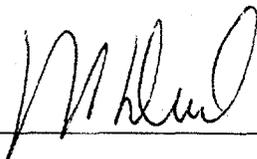
For products formulated to be added directly to cold water inside a hot steam vaporizer. [bullet] use 1 tablespoonful of solution for each quart of water or 1½ teaspoonsful of solution for each pint of water [bullet] add solution directly to cold water only in a hot steam vaporizer [bullet] follow manufacturer's directions for using vaporizer or *For products formulated to be placed in the medication chamber of a hot steam vaporizer.* [bullet] place water in the vaporizer and follow manufacturer's directions for using vaporizer [bullet] place solution in the medication chamber



only) [bullet] breathe in the medicated vapors [bullet] use up to three times daily or as directed
by a doctor [bullet] children under 2 years of age: Ask a doctor.

Dated: 7/21/00

July 21, 2000



Margaret M. Dotzel
Associate Commissioner for Policy

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