DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 89N-0525]

RIN 0905-AA06

Status of Certain Over-the-Counter Drug Category II and III Active Ingredients

AGENCY: Food and Drug Administration, HHS.

ACTION: Final rule.

SUMMARY: The Food and Drug Administration (FDA) is issuing a final rule establishing that certain active ingredients in over-the-counter (OTC) drug products are not generally recognized as safe and effective or are misbranded. FDA is issuing this final rule after considering the reports and recommendations of various OTC advisory review panels and public comments on the agency's notices of proposed rulemaking. Based on the absence of substantive comments in opposition to the agency's proposed nonmonograph status for these ingredients as well as the failure of interested parties to submit new data or information to FDA pursuant to 21 CFR 330.10(a)(7)(iii), the agency is issuing this final rule to remove from the OTC market these ingredients for the uses specified in this rule. This final rule is part of the ongoing review of OTC drug products conducted by FDA.

EFFECTIVE DATE: May 7, 1991.

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 various issues of the **Federal Register**, FDA has published, under § 330.10(a)(6) (21 CFR 330.10(a)(6)), advance notices of proposed rulemaking to establish monographs for specific classes of OTC drug products, together with the recommendations of the OTC advisory review panels, which were responsible for evaluating data on the active ingredients in the specific drug class(es) in each proposed monograph. Following publication of each proposed monograph, interested parties were invited to submit comments within a set time period, with an additional period of time allowed for reply comments in response to comments filed in the initial comment period.

After evaluation and consideration of the OTC advisory review panels' recommendations and the comments and reply comments received in response to the initial publication of the advance notices of proposed rulemaking, the agency's proposed regulations in the form of various tentative final monographs for specific classes of OTC drug products were published in the **Federal Register.** Interested persons were invited to file comments, objections, and/or requests for an oral hearing before the Commissioner of Food and Drugs regarding the specific proposals within a set time period. A period of 12 months was provided for the submission of new data and information regarding each specific proposed rulemaking, and 2 additional months were provided for comments on the new data to be submitted.

In the **Federal Register** of May 16, 1990 (55 FR 20434), FDA published, under § 330.10(a)(7)(ii) (21 CFR 330.10(a)(7)(ii)), a proposed rulemaking encompassing all Category II and Category III active ingredients for which the periods for submission of comments and new data following the publication of a notice of proposed rulemaking had closed and for which no significant comments or new data to upgrade the status of these ingredients had been submitted. In each instance, a final rule for the class of ingredients involved had not been published to date. Since that time, final rules for two of the OTC drug rulemakings included in the proposal, corn and callus remover drug products and wart remover drug products, have been published (August 14, 1990; 55 FR 33258 and 55 FR 33246, respectively). Accordingly, the active ingredients from those rulemakings that were included in the proposal are not included in this final rule.

The OTC drug review administrative procedures provide in § 330.10(a)(7)(ii) that the Commissioner may publish a separate tentative order proposing that active ingredients be excluded from an OTC drug monograph on the basis of the Commissioner's determination that they would result in a drug product not being generally recognized as safe and effective or would result in misbranding. This order may include active ingredients for which no substantial comments in opposition to the advisory panel's proposed classification and no new data and information were received pursuant to § 330.10(a)(6)(iv) (21 CFR 330.10(a)(6)(iv)). Section 330.10(a)(7)(ii) authorizes the publication of a separate tentative order immediately following the close of the comment and new data periods for an advance notice of proposed rulemaking. However, in the case of the ingredients included in the proposal, the Commissioner waited until after proposed rulemakings were published and the periods for submission of comments and new data had ended. This additional period allowed the fullest possible opportunity for public comment and receipt of new data to upgrade the status of these ingredients.

As mentioned, no substantive comments or new data were submitted to support reclassification of any of these active ingredients to monograph status. Therefore, before a final rule on each respective drug category is published, the Commissioner has determined that these ingredients are not generally recognized as safe and effective and that any OTC drug product containing any of these active ingredients not be allowed to continue to be initially introduced or initially delivered for introduction into interstate commerce unless it is the subject of an approved application. FDA has elected to act on these ingredients in advance of finalization of other monograph conditions in order to expedite completion of the OTC drug review. Table I below lists the title, docket number, and active ingredients of the specific rulemakings that are addressed in this final rule.

FDA advises that the active ingredients listed in this final rule will not be included in the relevant final monographs because they have not been shown to be generally recognized as safe and effective for their intended use. The agency is amending 21 CFR part 310 to list all of the active ingredients covered by this final rule by adding to subpart E new § 310.545 (21 CFR 310.545). The agency further advises that these active ingredients should be eliminated from OTC drug products by May 7, 1991, regardless of whether further testing is undertaken to justify future use, and regardless of whether the relevant OTC drug monographs have been finalized at that time. Therefore, on or after May 7, 1991, no OTC drug product containing any ingredient listed in § 310.545 either labeled or intended as an active ingredient for the uses specified in that section 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 containing an ingredient subject to this final rule that is repackaged or relabeled after the effective date of this final rule must be in compliance with the final rule regardless of the date the product was initially introduced or

initially delivered for introduction into interstate commerce. Manufacturers are urged to comply voluntarily with this final rule at the earliest possible date.

The agency points out that publication of this final rule does not preclude a manufacturer's testing an ingredient. New, relevant data can be submitted to the agency at a later date as the subject of an application that may provide for prescription or OTC marketing status. (See 21 CFR part 314.) As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in an appropriate citizen petition to amend or establish a monograph, as appropriate. (See 21 CFR 10.30.) However, marketing of products containing these active ingredients may not continue while the data are being evaluated by the agency.

In response to the proposed rule on certain OTC Category II and III ingredients, 12 drug manufacturers, 1 trade association, and 1 physician submitted comments. Copies of the comments received are on public display in the Dockets Management Branch (HFA–305), Food and Drug Administration, rm. 4–62, 5600 Fishers Lane, Rockville, MD 20857. 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.

I. The Agency's Conclusions on the Comments

1. One comment requested clarification of the status of allantoin which was listed as a Category III skin protectant in the May 16, 1990 proposal (55 FR 20434 at 20437).

A correction notice clarifying that allantoin is Category I as a skin protectant and is Category III for wound healing claims was published in the Federal Register on June 7, 1990 (55 FR 23234).

2. One comment requested that lobeline be added to the list of Category II and III smoking deterrent ingredients in the May 16, 1990 proposal. The comment felt that lobeline should be removed from the market due to a lack of proof of its effectiveness as a smoking deterrent.

Although lobeline is in Category III as an OTC smoking deterrent due to a lack of evidence of effectiveness (50 FR 27552 at 27555), substantial comment has been received by the agency on this ingredient. Evidence regarding its effectiveness is currently under review as part of the OTC smoking deterrent rulemaking (Docket No. 81N–0027). Lobeline was not included in the May 16, 1990 proposal because that notice was limited to those Category II and III ingredients for which no substantive comment had been received by the agency.

3. One comment mentioned its submission of July 24, 1987 to the proposed rulemaking on OTC dandruff, seborrheic dermatitis, and psoriasis drug products (Docket No. 82N–0214) regarding the use of menthol as a Category I antipruritic active ingredient in combination with coal tar, a Category I antidandruff active ingredient. The comment requested that the May 16, 1990 proposal be revised to exclude menthol because of the pending data submission. Alternatively, the comment requested that the rulemaking remain as written for menthol used exclusively in the treatment of dandruff and exclude menthol used as an antipruritic in combination with coal tar.

The inclusion of menthol as a Category III antidandruff ingredient in the May 16, 1990 proposal was not intended to apply to the use of menthol as an antipruritic in combination with coal tar. A footnote has been included in the table in this final rule clarifying that it does not apply to the use of menthol as an antipruritic when used in combination with the Category I antidandruff ingredient coal tar.

4. One comment requested that sulfur and ichthammol be deleted from the list of boil treatment drug product ingredients included in the May 16, 1990 proposal. The comment pointed out that on January 26, 1989, a substantive comment, including data and scientific references supporting the use of sulfur and ichthammol as active ingredients in the treatment of boils, was submitted to the proposed rulemaking on OTC boil treatment drug products (Docket No. 82N–0054).

The agency acknowledges this oversight. Sulfur and ichthammol had been classified in Category II in the advance notice of proposed rulemaking for OTC boil ointment drug products (47 FR 28306 at 28307 and 28308), but were classified in Category III in the tentative final monograph (53 FR 2198 at 2204). These ingredients have been deleted from the list of boil treatment ingredients included in this final rule.

5. One comment requested clarification of the agency's inclusion of povidone-iodine in the May 16, 1990 proposal. Specifically, the comment requested acknowledgement that povidone-iodine was not granted monograph status in the rulemaking proceedings for OTC dandruff, seborrheic dermatitis, and psoriasis drug products (Docket No. 82N–0214) and acne drug products (Docket No. 81N–0114) only because the manufacturers of povidone-iodine failed to submit data and/or comments on efficacy for such uses. The comment asserted a lack of commercial interest in developing such data, not evidence that povidone-iodine would be unsafe or ineffective for such uses.

Another comment requested clarification of the agency's inclusion of chloroxylenol in the May 16, 1990 proposal. Specifically, the comment requested acknowledgement that chloroxylenol was not granted monograph status in the rulemaking proceedings for OTC acne drug products (Docket No. 81N–0114) and OTC ingrown toenail drug products (Docket No. 80N–0348) because the manufacturers of chloroxylenol did not submit data and/or comments on safety and efficacy. The comment asserted that data were not submitted because of a lack of commercial interest, not because evidence suggested that chloroxylenol would be unsafe or ineffective for such uses.

The agency notes that no substantive comments or data on the effectiveness of povidone-iodine or chloroxylenol were submitted to the specific rulemakings listed by the comments. Accordingly, povidone-iodine and chloroxylenol are included in this final rule.

The agency is unable to state why manufacturers elected not to submit data on these ingredients for these uses. However, nonmonograph status for the indications included in this final rule has no bearing on the ingredients' inclusion in other OTC drug monographs covering other uses. As the comments noted, data on the ingredients' effectiveness for other uses may be submitted in the future in the form of a petition to amend the appropriate final monograph.

6. One comment requested clarification of the statement in the May 16, 1990 proposal that "FDA has determined that the presence of these ingredients in an OTC drug product would result in that drug product not being generally recognized as safe and effective or would result in misbranding," (55 FR 20434). The comment contended that this statement applies only to the use of nonmonograph ingredients as active ingredients. The comment stated that certain nonmonograph ingredients may be used as inactive ingredients and mentioned the use of sorbitol as a sweetening or flavoring agent in oral health care products. The comment asserted that the mere presence of a nonmonograph ingredient when used as an inactive

ingredient should not result in a misbranded product.

This final rule affects only the use of the listed ingredients as active ingredients for the specific indications listed. The agency has reviewed all of the ingredients covered by this final rule and recognizes that some of the ingredients have valid uses as inactive ingredients. Examples include: (1) Sorbitol, sugars, eucalyptol, and peppermint oil for sweetening, flavor, and aroma and (2) petrolatum and lanolin as ointment bases. Other ingredients listed below may also have valid uses as pharmaceutical necessities. This final rule does not affect such uses. However, any inactive ingredient present in the product should have an appropriate purpose and be safe and suitable for use in the product in accord with 21 CFR 330.1(e).

7. Three comments requested that the agency delay its proposed action regarding certain ingredients in OTC digestive aid drug products under this rulemaking. These comments stated that a major foreign manufacturer of a digestive aid drug product containing the enzymes pancreatin, papain, bromelain, trypsin, lipase, amylase, chymotrypsin, and rutoside intends to petition the agency in the near future to reopen the administrative record for OTC digestive aid drug products (Docket No. 81N-0106). The comment contended that this substantial commitment on the part of a foreign manufacturer to comply with FDA's requirements should not be obstructed by "house cleaning" efforts like the May 16, 1990 proposal, and this manufacturer will provide relevant information on these products.

Another comment requested that the ingredient acetic acid be deleted from the list of active ingredients in topical otic drug products (Docket No. 77N-334S) covered by this final rule. The comment included a citizen petition to reopen the administrative record for topical otic drug products to accept data regarding the safety and effectiveness of acetic acid for the prevention of swimmer's ear.

Another comment requested that the agency delete calcium carbonate from the list of antidiarrheal drug ingredients affected by this rulemaking to allow additional time to assemble evidence of its effectiveness.

The agency clearly stated in the May 16, 1990 proposal that "This proposal does not constitute a reopening of the administrative record or an opportunity to submit new data to any of the specific rulemakings," (55 FR 20434). In addition, § 330.10(a)(7)(v) (21 CFR 330.10(a)(7)(v)) of the regulations governing the OTC drug review states that new data and information submitted after the closing of the administrative record for a tentative final rule " * * * but prior to the establishment of a final monograph will be considered as a petition to amend the monograph and will be considered by the Commissioner only after a final monograph has been published in the **Federal Register** unless the Commissioner finds that good cause has been shown that warrants earlier consideration."

None of the comments offered good cause why the requested ingredients should not be included in this final rule. Of the eight enzymes contained in the digestive aid drug product mentioned by the first three comments, only two, pancreatin and papain, are included in this final rule. There have been no data submissions to date on these ingredients. Of the remaining six enzymes, only two, amylase and lipase, are still under consideration in the OTC digestive aids rulemaking. No data have been submitted to the OTC drug review on the remaining four enzymes—bromelain, trypsin, chymotrypsin, and rutoside; thus, these ingredients are not currently under consideration in the OTC digestive aids rulemaking. Further, the specific drug product containing these eight enzymes is not currently marketed in the United States.

The comment and accompanying petition regarding acetic acid likewise fails to offer either any explanation as to why the data contained in the petition were not submitted prior to the closing of the administrative record or any good cause for reopening the administrative record for OTC topical otic drug products (Docket No. 77N-334S). The petition included published reports of clinical trials and other information to support the safety and effectiveness of acetic acid for the prevention of swimmer's ear.

The agency has reviewed the existing administrative record of the rulemaking for OTC topical otic drug products for the prevention of swimmer's ear and determined that some of the data submitted by the comment have already been considered in that rulemaking and were found to be inadequate to support monograph status. The additional information provided is also insufficient to support monograph status. Finally, as noted above, the rulemaking covered by this final rule is not the proper forum to submit additional data to support safety and effectiveness of any specific ingredient. Therefore, the request to suspend or delay that portion of this final rule as relates to acetic acid for the prevention of swimmer's ear is denied.

The comment regarding calcium carbonate did not contain any statement as to why the firm failed to submit data on this ingredient during the 15 years since the publication of the advance notice of proposed rulemaking on OTC antidiarrheal drug products on March 21, 1975 (Docket No. 78N-036D). The agency has examined the administrative record for this rulemaking and finds no record of any previous comments or data submissions on calcium carbonate. Accordingly, the request to delete calcium carbonate for antidiarrheal use from this final rule is denied.

While the agency may consider the data offered by the comments, such data must be submitted in the form of a petition to amend the appropriate final monograph in accordance with § 10.30 (21 CFR 10.30) and must be addressed to the rulemaking for the appropriate drug category.

8. Two comments requested that a February 7, 1983 petition to reopen the administrative record on OTC skin protectant drug products (Docket No. 78N-0021, Comment No. C00029) also be regarded as a substantive comment to the OTC dandruff, seborrheic dermatitis, and psoriasis rulemaking (Docket No. 82N-0214). The comments stated that the manufacturer that submitted the February 7, 1983 petition assumed (erroneously) that its petition would automatically be entered into all appropriate dockets and therefore did not enter the appropriate docket numbers at the heading of the petition. The comments further pointed out that the Advisory Review Panel on OTC Miscellaneous External Drug Products considered colloidal oatmeal only for a dandruff claim and not for relief of itching due to psoriasis, even though such itching claims were made on colloidal oatmeal products. The comments added that the 1983 petition specifically included label claims for relief of "itchy, sore, sensitive skin due to * * * eczemal psoriasis." The comments, therefore, requested that the February 7, 1983 petition to the rulemaking for OTC skin protectant drug products (Docket No. 78N-0021, Comment No. C00029) also be regarded as a substantive comment to the rulemaking for OTC dandruff, seborrheic dermatitis, and psoriasis drug products (Docket No. 82N-0214), that colloidal oatmeal continue to be evaluated as part of that rulemaking, and that colloidal oatmeal be deleted from the list of OTC dandruff, seborrheic dermatitis, and psoriasis ingredients affected by this final rule.

While the comments correctly point out that the heading of the petition fails

to list any docket number(s), there is no indication that the petition was ever intended to address any rulemaking other than the one for OTC skin protectant drug products. The petition clearly identifies a docket and rulemaking in its first paragraph, where it states that this petition is "* * * to request the Commissioner of Food and Drugs ("Commissioner") to reopen the administrative record on Skin Protectant Drug Products for Over-the-Counter Human Use to allow for the consideration of colloidal oatmeal as generally recognized as a safe and effective skin protectant. Proposed 21 CFR 347, Docket 78N-0021, 43 FR 34628, *et seq.* (August 4, 1978)."

No request is made anywhere in the petition for consideration under any other rulemaking. In addition, if this petition was also intended as a comment to the rulemaking for OTC dandruff, seborrheic dermatitis, and psoriasis drug products, it could have been included as a comment in the administrative record for that rulemaking until May 4, 1983 when the record closed. Also, it could have been included during the 12 months that the administrative record was open following publication of the tentative final monograph for OTC dandruff, seborrheic dermatitis, and psoriasis drug products on July 30, 1986 (51 FR 27346).

The agency further notes that the comment in question deals solely with the use of colloidal oatmeal for the temporary relief of itching from a wide variety of skin conditions and contains no data on the use of colloidal oatmeal when used alone in the treatment of psoriasis. As indicated in the discussion of the use of hydrocortisone for the relief of itching in comment 13 of the tentative final monograph for OTC dandruff, seborrheic dermatitis, and sporiasis drug products (51 FR 27346 at 27351), claims for temporary symptomatic relief of itching are not appropriate for inclusion under that monograph. Therefore, the comments' request to delete colloidal oatmeal from the list of OTC dandruff, seborrheic dermatitis, and psoriasis ingredients included in this final rule is denied. New data on the safety and effectiveness of colloidal oatmeal in the relief of itching from a variety of causes and conditions including psoriasis may be submitted in the future in the form of a petition to amend the external analgesic, skin protectant, or other appropriate monographs.

9. One comment submitted a paper entitled "Virucidal and Bactericidal Effects of Ascorbic Acid" (Ref. 1), which included a bibliography with 30 references. The comment noted the Category II status of ascorbic acid as a corn and callus remover and its Category III status as a wart remover. The comment contended that the virucidal and bactericidal effects of ascorbic acid may be useful in topical applications, particularly in wart remover products.

As noted above, final rules for OTC corn and callus remover drug products and OTC wart remover drug products were published on August 14, 1990. Ascorbic acid was not included in either final monograph. Any data supporting the use of ascorbic acid in either of these types of products needs to be submitted in the form of a petition to amend a final monograph in accord with 21 CFR 330.10(a)(12).

The report submitted by the comment examines the effects of exposing viruses and bacteria to ascorbic acid. It does not contain any clinical data in which a product containing ascorbic acid was used as a corn and callus remover or a wart remover. The agency concludes that this report is inadequate to support monograph status for ascorbic acid for either of these uses.

Reference

(1) Comment No. 12, Docket No. 89N-0525, Dockets Management Branch.

II. Summary of Significant Changes From the Proposed Rule

1. A statement has been added clarifying that menthol, when used as an antipruritic in combination with the antidandruff ingredient coal tar, is not covered by this final rule (see comment 3 above).

2. Sulfur and ichthammol have been deleted from the list of boil treatment drug product active ingredients covered by this final rule (see comment 4 above.)

3. In reexamining the administrative record of the rulemaking for OTC topical otic drug products (Docket No. 77N-334S), a substantive comment regarding anhydrous glycerin was inadvertently overlooked (Comment No. RPT-002). Therefore, anhydrous glycerin has been deleted from the list of topical otic drug product active ingredients affected by this final rule.

4. The term "active" has been included in the hearing of table I to clarify that this final rule pertains to use of the listed ingredients as active ingredients in the applicable OTC drug rulemakings.

5. New § 310.545 (21 CFR 310.545) has been included to list all of the active ingredients covered by this final rule.

III. The Agency's Final Conclusions on Certain OTC Drug Category II and III Active Ingredients

The agency has determined that no substantive comments or additional data have been submitted to the OTC drug review to support any of the ingredients listed below as being generally recognized as safe and effective for the OTC drug uses specified in the table (Table I). Based on the agency's procedural regulations (21 CFR 330.10(a)(7)(ii)), the agency has determined that these ingredients are not generally recognized as safe and effective and are misbranded when present in the following specific OTC drug products:

TABLE 1.—OTC DRUG RULEMAKINGS AND ACTIVE INGREDIENTS COVERED BY THIS NOTICE

Rulemaking
(1) Topical Acne Drug Products (Docket No. 81N-0114):
Alcloxa
Alkyl isoquinolinium bromide
Aluminum chlorohydrex
Aluminum hydroxide
Benzocaine
Benzoic acid
Boric acid
Calcium polysulfide
Calcium thiosulfate
Camphor
Chlorhydroxyquinoline
Chloroxylenol
Coal tar
Dibenzothiophene
Estrone
Magnesium aluminum silicate
Magnesium sulfate
Phenol
Phenolate sodium
Phenyl salicylate
Povidone iodine
Pyrilamine maleate
Resorcinol (as single ingredient)
Resorcinol monoacetate (as single ingredient)
Salicylic acid (over 2 up to 5 percent)
Sodium borate
Sodium thiosulfate
Tetracaine hydrochloride
Thymol
Vitamin E
Zinc oxide
Zinc stearate
Zinc sulfide
(2) Anticaries drug products (Docket No. 80N-0042):
Acidulated sodium phosphate
Hydrogen fluoride
Sodium carbonate

TABLE 1.—OTC DRUG RULEMAKINGS AND ACTIVE INGREDIENTS COVERED BY THIS NOTICE—Continued

Rulemaking
Sodium monofluorophosphate (6 percent rinse)
Sodium phosphate
(3) Antidiarrheal drug products (Docket No. 78N-0036D):
Aluminum hydroxide
Atropine sulfate
Calcium carbonate
Carboxymethylcellulose
Glycine
Homatropine methylbromide
Hyoscyamine sulfate
Lactobacillus acidophilus
Lactobacillus bulgaricus
Opium, powdered
Opium tincture
Paregoric
Phenyl salicylate
Scopolamine hydrobromide
Zinc phenolsulfonate
(4) Antiperspirant drug products (Docket No. 78N-0064):
Alum, potassium
Aluminum bromohydrate
Aluminum chloride (alcoholic solutions)
Aluminum chloride (aqueous solution) (aerosol only)
Aluminum sulfate
Aluminum sulfate, buffered (aerosol only)
Sodium aluminum chlorohydroxy lactate
(5) Boil treatment drug products (Docket No. 82N-0054):
Aminacrine hydrochloride
Bismuth subnitrate
Calomel
Camphor
Cholesterol
Ergot fluidextract
Hexachlorophene
Isobutamben
Juniper tar
Lanolin
Magnesium sulfate
Menthol
Methyl salicylate
Oxyquinoline sulfate
Petrolatum
Phenol
Pine tar
Rosin
Rosin cerate
Sassafras oil
Thymol
Zinc oxide
(6) Cold, cough, allergy, bronchodilator, and antiasthmatic drug products:
(A) Antihistamine drug products (Docket No. 76N-052H):
Methapyrilene hydrochloride
Methapyrilene fumarate
Thenyldiamine
(B) Nasal decongestant drug products (Docket No. 76N-052N):
Allyl isothiocyanate
Camphor (lozenge)
Creosote, beechwood (oral)
Eucalyptol (lozenge)
Eucalyptol (mouthwash)
Eucalyptus oil (lozenge)
Eucalyptus oil (mouthwash)
Menthol (mouthwash)
Peppermint oil (mouthwash
Thenyldiamine
Thymol
Thymol (lozenge)
Thymol (mouthwash)
Turpentine oil
(7) Dandruff/seborrheic dermatitis/psoriasis drug products (Docket No. 82N-0214):
Alakyl isoquinolinium
Allantoin
Benzalkonium chloride
Benzethonium chloride
Boric acid
Calcium undecylenate
Captan
Chloroxylenol
Colloidal oatmeal
Cresol, saponated
Ethohexadiol
Eucalyptol
Juniper tar
Lauryl isoquinolinium
Methol [1]
Mercury oleate
Methylbenzethonium
Methyl salicylate
Phenol
Phenolate sodium
Pine tar
Povidone-iodine
Resorcinol
Sodium borate
Sodium salicylate
Thymol
Undecylenic acid
(8) Digestive aid drug products (Docket No. 81N-0106):
Bismuth sodium tartrate
Calcium carbonate
Cellulase
Dehydrocholic acid
Dihydroxyaluminum
Duodenal substance
Garlic, dehydrated
Glutamic acid
Hemicellulase
Homatropine
Magnesium hydroxide
Magnesium trisilicate
Ox bile extract
Pancreatin
Pancrelipase
Papain
Peppermint oil
Pepsin
Sodium bicarbonate
Sodium citrate
Sorbitol
(9) Exocrine pancreatic insufficiency drug products (Docket No. 79N-0379):
Hemicellulase
(10) External analgesic drug products (Docket No. 78N-0301):
(A) Analgesic and anesthetic drug products
Aspirin
Chloral hydrate
Chlorobutanol
Cyclomethycaine sulfate
Eugenol
Hexylresorcinol
Methapyrilene hydrochloride
Salicylamide
Thymol
(B) Counterirritant drug products:
Chloral hydrate
Eucalyptus oil
(C) Male genital desensitizer drug products
Benzyl alcohol
Camphorated metacresol
Ephedrine hydrochloride
(11) Ingrown toenail relief drug products (Docket No. 80N-0348):
Chloroxylenol
Urea
(12) Laxative drug products (Docket No. 78N-036L):
(A) Bulk laxatives
Agar
Carrageenan (degraded)
Carrageenan (native)
Guar gum
(B) Saline laxative
Tartaric acid
(C) Stool softener
Poloxamer 188
(D) Stimulant laxatives
Aloin
Bile salts/acids
Calcium pantothenate
Calomel
Colocynth
Elaterin resin
Frangula
Gamboge
Ipomea
Jalap
Ox bile
Podophyllum resin
Prune concentrate
Prune powder
Rhubarb, chinese
Sodium oleate
(13) Nailbiting and thumbsucking deterrent drug products (Docket No. 80N-0146):
Denatonium benzoate
(14) Oral health care drug products (nonantimicrobial) (Docket No. 81N-0033):
Antipyrine
Camphor
Cresol
Dibucaine
Dibucaine hydrochloride
Eucalyptol

TABLE 1.—OTC DRUG RULEMAKINGS AND ACTIVE INGREDIENTS COVERED BY THIS NOTICE—Continued

Rulemaking
Lidocaine
Lidocaine hydrochloride
Methyl salicylate
Myrrh tincture
Pyrilamine maleate
Sorbitol
Sugars
Tetracaine
Tetracine hydrochloride
Thymol
(15) Topical otic drug products for the prevention of swimmer's ear (Docket No. 77N-334S):
Acetic acid
(16) Poison treatment drug products (Docket No. 81N-0050):
Ipecac fluidextract
Ipecac tincture
Zinc sulfate
(17) Skin bleaching drug products (Docket No. 78N-0065):
Mercury, ammoniated
(18) Skin protectant drug products (Docket No. 78N-0021):
Sulfur Allantoin (wound healing claims only)
Tannic acid
Zinc acetate (wound healing claims only)
(19) Smoking deterrent drug products (Docket No. 81N-0027):
Clove
Coriander
Eucalyptus oil
Ginger, jamaica
Lemon oil, terpeneless
Licorice root extract
Menthol
Methyl salicylate
Quinine ascorbate
Silver nitrate
Thymol

[1] Does not apply to the use of menthol as an antipruritic when used in combination with the Category I antidandruff ingredient coal tar.

Accordingly, any drug product containing any of these active ingredients and labeled for the OTC use identified above will be considered nonmonograph and misbranded under section 502 of the Federal Food, Drug, and Cosmetic Act (the act) (21 U.S.C. 352) and a new drug under section 201(p) of the act (21 U.S.C. 321(p)) for which an approved application under section 505 of the act (21 U.S.C. 355) and 21 CFR part 314 of the regulations is required for marketing. As an alternative, where there are adequate data establishing general recognition of safety and effectiveness, such data may be submitted in a citizen petition to amend the appropriate monograph to include any of the above active ingredients in OTC drug products. (See 21 CFR 10.30.)

Any OTC drug product containing any of the above ingredients either labeled or intended as an active ingredient for the uses included in the above rulemakings that is initially introduced or initially delivered for introduction into interstate commerce after May 7, 1991, and that is not the subject of an approved application will be in violation of sections 502 and 505 of the act (21 U.S.C. 352 and 355) and, therefore, subject to regulatory action. Further, any OTC drug product containing an ingredient subject to this rulemaking that is repackaged or relabeled after May 7, 1991, must be in compliance with the rule regardless of the date the product was initially introduced or initially delivered for introduction into interstate commerce. Manufacturers are encouraged to comply voluntarily with the rule at the earliest possible date.

No comments were received in response to the agency's request for specific comment on the economic impact of this rulemaking (55 FR 20434 at 20438). The agency concludes that there is no basis for the continued marketing of these ingredients for the uses listed in Table I above. There are other ingredients being considered for monograph status that manufacturers can use to reformulate affected products. In many instances, manufacturers have already reformulated their products to include these ingredients. As a result of this final rule, manufacturers may need to reformulate some products prior to promulgation of the applicable final monograph. However, there will be no additional costs because reformulation would be required, in any event, when the final monograph is published.

Early finalization of the nonmonograph status of the ingredients listed in this notice will benefit both consumers and manufacturers. Consumers will benefit from the early removal from the marketplace of ingredients for which safety and effectiveness have not been established. This will result in a direct economic savings to consumers. Manufacturers will benefit from being able to use alternative ingredients that are being considered as being found generally recognized as safe and effective without incurring additional expense of clinical testing for these ingredients. Based on the above, the agency certified 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 in 21 CFR Part 310

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and the Administrative Procedure Act, subchapter D of chapter I of title 21 of the Code of Federal Regulations is amended in part 310 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 added to subpart E to read as follows:

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

(a) A number of active ingredients have been present in OTC drug products for various uses, as described below. However, based on evidence currently available, there are inadequate data to establish general recognition of the safety and effectiveness of these ingredients for the specified uses:

(1) *Topical acne drug products.*

Alcloxa
Alkyl isoquinolinium bromide
Aluminum chlorohydrex
Aluminum hydroxide
Benzocaine
Benzoic acid
Boric acid
Calcium polysulfide
Calcium thiosulfate
Camphor
Chlorhydroxyquinoline
Chloroxylenol
Coal tar
Dibenzothiophene
Estrone
Magnesium aluminum silicate
Magnesium sulfate
Phenol
Phenolate sodium
Phenyl salicylate
Povidone-iodine
Pyrilamine maleate
Resorcinol (as single ingredient)
Resorcinol monoacetate (as single ingredient)
Salicylic acid (over 2 up to 5 percent)
Sodium borate
Sodium thiosulfate
Tetracaine hydrochloride
Thymol
Vitamin E
Zinc oxide
Zinc stearate

Zinc sulfide

(2) *Anticaries drug products.*

Acidulated sodium phosphate
Hydrogen fluoride
Sodium carbonate
Sodium monofluorophosphate (6 percent rinse)
Sodium phosphate

(3) *Antidiarrheal drug products.*

Aluminum hydroxide
Atropine sulfate
Calcium carbonate
Carboxymethylcellulose
Glycine
Homatropine methylbromide
Hyoscyamine sulfate
Lactobacillus acidophilus
Lactobacillus bulgaricus
Opium, powdered
Opium tincture
Paregoric
Phenyl salicylate
Scopolamine hydrobromide
Zinc phenolsulfonate

(4) *Antiperspirant drug products.*

Alum, potassium
Aluminum bromohydrate
Aluminum chloride (alcoholic solutions)
Aluminum chloride (aqueous solution) (aerosol only)
Aluminum sulfate
Aluminum sulfate, buffered (aerosol only)
Sodium aluminum chlorohydroxy lactate

(5) *Boil treatment drug products.*

Aminacrine hydrochloride
Bismuth subnitrate
Calomel
Camphor
Cholesterol
Ergot fluidextract
Hexachlorophene
Isobutamben
Juniper tar
Lanolin
Magnesium sulfate
Menthol
Methyl salicylate
Oxyquinoline sulfate
Petrolatum
Phenol
Pine tar
Rosin
Rosin cerate
Sassafras oil
Thymol
Zinc oxide

(6) *Cold, cough, allergy, bronchodilator, and antiasthmatic drug products*—(i) *Antihistamine drug products.*

Methapyrilene hydrochloride
Methapyrilene fumarate
Thenyldiamine

(ii) *Nasal decongestant drug products.*

Allyl isothiocyanate
Camphor (lozenge)
Creosote, beechwood (oral)
Eucalyptol (lozenge)
Eucalyptol (mouthwash)
Eucalyptus oil (lozenge)
Eucalyptus oil (mouthwash)
Menthol (mouthwash)
Peppermint oil (mouthwash)
Thenyldiamine
Thymol
Thymol (lozenge)
Thymol (mouthwash)
Turpentine oil

(7) *Dandruff/seborrheic dermatitis/psoriasis drug products.*

Alkyl isoquinolinium
Allantoin
Benzalkonium chloride
Benzethonium chloride
Boric acid
Calcium undecylenate
Captan
Chloroxylenol
Colloidal oatmeal
Cresol, saponated
Ethohexadiol
Eucalyptol
Juniper tar
Lauryl isoquinolinium
Methol (Does not apply to the use of menthol as an antipruritic when used in combination with the Category I antidandruff ingredient coal tar)
Mercury oleate
Methylbenzethonium
Methyl salicylate
Phenol
Phenolate sodium
Pine tar
Providone-isodine
Resorcinol
Sodium borate
Sodium salicylate
Thymol
Undecylenic acid

(8) *Digestive aid drug products.*

Bismuth sodium tartrate
Calcium carbonate
Cellulase
Dehydrocholic acid
Dihydroxyaluminum
Duodenal substance
Garlic, dehydrated
Glutamic acid
Hemicellulase
Homatropine
Magnesium hydroxide
Magnesium trisilicate
Ox bile extract
Pancreatin
Pancrelipase
Papain
Peppermint oil
Pepsin
Sodium bicarbonate
Sodium citrate
Sorbitol

(9) *Exocrine pancreatic insufficiency drug products.*

Hemicellulase

(10) *External analgesic drug products*—(i) *Analgesic and anesthetic drug products.*

Aspirin
Chloral hydrate
Chlorobutanol
Cyclomethycaine sulfate
Eugenol
Hexylresorcinol
Methapyrilene hydrochloride
Salicylamide
Thymol

(ii) *Counterirritant drug products.*

Chloral hydrate
Eucalyptus oil

(iii) *Male genital desensitizer drug products.*

Benzyl alcohol
Camphorated metacresol
Ephedrine hydrochloride

(11) *Ingrown toenail relief drug products.*

Chloroxylenol
Urea

(12) *Laxative drug products*—(i) *Bulk laxatives.*

Agar
Carrageenan (degraded)
Carrageenan (native)
Guar gun

(ii) *Saline laxative.*

Tartaric acid

(iii) *Stool softener.*

Poloxamer 188

(iv) *Stimulant laxatives.*

Aloin
Bile salts/acids
Calcium pantothenate
Calomel
Colocynth
Elaterin resin
Frangula
Gamboge
Ipomea
Jalap
Ox bile
Podophyllum resin
Prune concentrate
Prune powder
Rhubarb, Chinese
Sodium Oleate

(13) *Nailbiting and thumbsucking deterrent drug products.*

Denatonium benzoate

(14) *Oral health care drug products (nonantimicrobial).*

Antipyrine
Camphor
Cresol
Dibucaine
Dibucaine hydrochloride
Eucalyptol
Lidocaine
Lidocaine hydrochloride
Methly salicylate
Myrrh tincture
Pyrilamine maleate
Sorbitol
Sugars
Tetracaine
Tetracaine hydrochloride
Thymol

(15) *Topical otic drug products for the prevention of swimmer's ear.*

Acetic acid

(16) *Poison treatment drug products.*

Ipecac fluidextract
Ipecac tincture
Zinc sulfate

(17) *Skin bleaching drug products.*

Mercury, ammoniated

(18) *Skin protectant drug products.*

Allantoin (wound healing claims only)
Sulfur
Tannic acid
Zinc acetate (wound healing claims only)

(19) *Smoking deterrent drug products.*

Clove
Coriander
Eucalyptus oil
Ginger, Jamaica
Lemon oil, terpeneless
Licorice root extract
Menthol
Methyl salicylate
Quinine ascorbate
Silver nitrate
Thymol

(b) Any OTC drug product that is labeled, represented, or promoted for the uses specified and containing any active ingredient(s) as specified in paragraph (a) of this section is regarded as a new drug within the meaning of section 210(p) of the Federal Food, Drug, and Cosmetic Act (the act), for which an approved new drug application under section 505 of the act and part 314 of this chapter is required for marketing. In the absence of an approved new drug application, such product is also misbranded under section 502 of the act.

(c) Clinical investigations designed to obtain evidence that any drug product labeled, represented, or promoted for the OTC uses and containing any active ingredient(s) as specified in paragraph (a) of this section is safe and effective for the purpose intended must comply with the requirements and procedures governing the use of investigational new drugs set forth in part 312 of this chapter.

(d) After May 7, 1991, any such OTC drug product initially introduced or initially delivered for introduction into interstate commerce that is not in compliance with this section is subject to regulatory action.

Dated: October 1, 1990.

James S. Benson,

Acting Commissioner of Food and Drugs.

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