DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

21 CFR Part 310

[Docket No. 91N-0505]

RIN 0905-AA06

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

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice of proposed rulemaking.

SUMMARY: The Food and Drug Administration (FDA) is issuing a notice of proposed rulemaking stating that certain ingredients in over-the-counter (OTC) drug products are not generally recognized as safe and effective or are misbranded. FDA is issuing this notice of proposed rulemaking after considering the reports and recommendations of various OTC advisory review panels and public comments on the agency's proposed regulations, which were issued in the form of a tentative final monograph (proposed rule). 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), 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. This proposal is part of the ongoing review of OTC drug products conducted by FDA.

DATES: Written comments, objections, or requests for oral hearing on the proposal before the Commissioner of Food and Drugs by October 26, 1992. Written comments on the agency's economic impact determination by October 26, 1992.

ADDRESSES: Written comments, objections, or requests for oral hearing to the Dockets Management Branch (HFA-305), Food and Drug Administration, rm. 1-23, 12420 Parklawn Dr., Rockville, MD 20857.

FOR FURTHER INFORMATION CONTACT: William E. Gilbertson, Center for Drug Evaluation and Research (HFD-810), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-295-8000.

SUPPLEMENTARY INFORMATION: In the **Federal Register** of November 7, 1990 (55 FR 46914), FDA published under § 330.10(a)(7)(ii) (21 CFR 330.10(a)(7)(ii)), a final rule on the status of certain OTC drug Category II and III active ingredients. That final rule declared as not generally recognized as safe and effective certain Category II and Category III active ingredients for which, under the agency's OTC drug review, 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.

At that time, there were other OTC drug review rulemakings for which the period for submission of comments and/or new data was still pending. Those periods have now closed, and there are a number of active ingredients for which no significant comments or new data were submitted. In each instance, a final rule for the class of ingredients involved has not been published to date. This proposal addresses the Category II and Category III active ingredients in those classes of ingredients, as discussed below.

This proposal also addresses a number of active ingredients that were considered in the rulemaking for OTC digestive aid drug products. In the advance notice of proposed rulemaking for those drug products (47 FR 454, January 5, 1982), a number of ingredients are listed for which the Advisory Review Panel on OTC Miscellaneous Internal Drug Products was neither able to locate nor was aware of any significant body of data demonstrating safety and effectiveness. These ingredients were not included in the final rule discussed above that was published on November 7, 1990. No comments or data have been submitted for any of these ingredients. Based on this lack of data, the agency is proposing these ingredients to be nonmonograph for safety and effectiveness and is adding them to the list already included in 21 CFR 310.545.

Under the OTC drug review administrative procedures (§ 330.10(a)(7)(ii)), the Commissioner of Food and Drugs (the Commissioner) may publish a separate tentative order covering active ingredients that have been reviewed and may propose that these 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)). While § 330.10(a)(7)(ii) authorizes the publication of a separate tentative order immediately following the close of the comment period and new data period for an advance notice of proposed rulemaking, the Commissioner has waited in the case of these ingredients until after proposed rulemakings were published and the periods for submission of comments and new data have ended, to allow for the fullest possible opportunity for public comment and receipt of new data in support of upgrading the status of these ingredients.

As mentioned, no substantive comments or new date were submitted to support reclassification of any of these ingredients to monograph status. Therefore, before a final rule on each respective drug category is published, the Commissioner is proposing that these ingredients be found not generally recognized as safe and effective and that any OTC drug product containing any of these 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. Manufacturers are encouraged to comply voluntarily at the earliest possible date.

Table I below lists the titles and docket numbers of the specific rulemakings containing active ingredients that are addressed in this document, together with the publication dates of the advance notice of proposed rulemaking (ANPRM) and the notice of proposed rulemaking (NPRM), as well as the closing dates for comments and submission of new data for each rulemaking. This proposal does not constitute a reopening of the administrative record or an opportunity to submit new data to any of the specified rulemakings. A citizen petition to reopen the administrative record of any specific rulemaking, whether or not such petition is accompanied by new data, will not be accepted as a comment to this rulemaking. Should an interested person submit a comment indicating that substantive comments or new data were previously submitted to the administrative record for any of the specified rulemakings, the agency will review the record for that rulemaking

and make a determination whether the affected ingredient shall continue to be evaluated under that specified rulemaking or be included in the final rule that will issue pursuant to this proposed rule.

FDA advises that the active ingredients discussed in this document (see Table II below) 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 further advises that these ingredients should be eliminated from OTC drug products 6 months after the date of publication in the **Federal Register** of a final rule in this proceeding regarding their status, 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. The OTC drug review administrative procedures provide that any new data and information submitted after the administrative record has closed following publication of a tentative final monograph (notice of proposed rulemaking), but prior to the establishment of a final monograph, 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. (See 21 CFR 330.10(a)(7)(v).)

The agency points out that publication of a final rule under this proceeding 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 a new drug application (NDA) 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.)

TABLE I.—OTC DRUG RULEMAKINGS COVERED BY THIS NOTICE

Rulemaking and action	Publication date	Comment closing date	New data closing date
(1) Digestive Aid Drug Products: (Docket No. 81N-0106)			
ANPRM	January 5, 1982	July 5, 1982	Not Applicable (N/A).
NPRM	January 29, 1988	March 29, 1988	March 29, 1989.
(2) Topical Antifungal Drug Products:			
(i) Topical Antifungal Drug Products: (Docket No. 80N-0476)			
ANPRM	March 23, 1982	July 21, 1982	N/A.
NPRM	December 12, 1989	March 12, 1990	February 12, 1991.
(ii) Diaper Rash Drug Products: (Docket No. 80N-476D)			
ANPRM	September 7, 1982	January 5, 1983	N/A.
NPRM	June 20, 1990	December 17, 1990	August 20, 1991.
(3) External Analgesic Drug Products:			
(i) Diaper Rash Drug Products: (Docket No. 78N-301D)			
ANPRM	September 7, 1982	January 5, 1983	N/A.
NPRM	June 20, 1990	December 17, 1990	August 20, 1991.
(ii) Fever Blister and Cold Sore Treatment Drug Products: (Docket No. 78N-301F)			
ANPRM	September 7, 1982	January 5, 1983	N/A.
NPRM	January 31, 1990	May 31, 1990	April 1, 1991.
(iii) Insect Bite and Sting Drug Products: (Docket No. 78N-301P)			
ANPRM	September 7, 1982	January 5, 1983	N/A.
NPRM	October 3, 1989	January 31, 1990	December 3, 1990.
(iv) Poison Ivy, Poison Oak, and Poison Sumac Drug Products: (Docket No. 78N-301P)			
ANPRM	September 7, 1982	January 5, 1983	N/A.
NPRM	October 3, 1989	January 31, 1990	December 3, 1990.
(4) Internal Analgesic, Antipyretic Antirheumatic Drug Products: (Docket No. 77N-0094)			
ANPRM	July 8, 1977	February 6, 1978	N/A.
NPRM	November 16, 1988	May 16, 1989	January 16, 1990.
(5) Orally Administered Menstrual Drug Products: (Docket No. 82N-0165)			
ANPRM	December 7, 1982	April 6, 1983	N/A.
NPRM	November 16, 1988	March 16, 1989	January 16, 1990.
(6) Pediculicide Drug Products: (Docket No. 81N-0201)			
ANPRM	June 29, 1982	October 27, 1982	N/A.
NPRM	April 3, 1989	June 2, 1989	June 4, 1990.
(7) Skin Protectant Drug Products:			
(i) Astringent Drug Products: (Docket No. 78N-021A)			
ANPRM	September 7, 1982	January 5, 1983	N/A.
NPRM	April 3, 1989	June 2, 1989	June 4, 1990.
(ii) Diaper Rash Drug Products: (Docket No. 78N-021D)			
ANPRM	September 7, 1982	January 5, 1983	N/A.
NPRM	June 20, 1990	December 17, 1990	August 20, 1991.
(iii) Fever Blister and Cold Sore Treatment Drug Products: (Docket No. 78N-021F)			
ANPRM	September 7, 1982	January 5, 1983	N/A.
NPRM	January 31, 1990	May 31, 1990	April 1, 1991.
(iv) Insect Bite and Sting Drug Products: (Docket No. 78N-021P)			
ANPRM	September 7, 1982	January 5, 1983	N/A.
NPRM	October 3, 1989	January 31, 1990	December 3, 1990.
(v) Poison Ivy, Poison Oak, and Poison Sumac Drug Products: (Docket No. 78N-021P)			
ANPRM	September 7, 1982	January 5, 1983	N/A.
NPRM	October 3, 1989	January 31, 1990	December 3, 1990.

I. OTC Drug Category II and III Ingredients

Based on the criteria discussed above, FDA is proposing that the following ingredients are not generally recognized as safe and effective and are misbranded when labeled as OTC drugs for the following uses:

TABLE II.—INGREDIENTS COVERED BY THIS NOTICE

Rulemaking and ingredients	Ingredient classification	
	ANPRM	NPRM
(1) Digestive aid drug products:		
Alcohol	II	II
Aluminum hydroxide	II	III
Amylase	II	II
Anise seed	II	II
Aromatic powder	II	II
Asafetida	II	II
Aspergillus oryza enzymes	II	II
Bacillus acidophilus	II	II
Bean	II	II
Belladonna alkaloids	II	II
Belladonna leaves, powdered extract.	II	II
Betaine hydrochloride	II	II
Bismuth subcarbonate	II	II
Bismuth subgallate	II	II
Black radish powder	II	II
Buckthorn	II	II
Calcium gluconate	II	II
Capsicum	II	II
Capsicum, fluid extract of	II	II
Carbon	II	II
Cascara sagrada extract	II	II
Catechu, tincture	II	II
Catnip	II	II
Chamomile flowers	II	II
Charcoal, wood	II	II
Chloroform	II	II
Cinnamon oil	II	II
Cinnamon tincture	II	II
Citrus pectin	II	II
Cnicus benedictus (blessed thistle).	II	II
Diastase	II	II
Diastase malt	II	II
Dog grass	II	II
Elecampane	II	II
Ether	II	II
Fennel acid	II	II
Galega	II	II
Ginger	II	II
Glycine	II	II
Hectorite	II	II
Horsetail	II	II
Huckleberry	II	II
Hydrastis canadensis (golden seal).	II	II
Hydrastis fluid extract	II	II
Hydrochloric acid	II	II
Iodine	II	II
Iron ox bile	II	II
Johnswort	II	II
Juniper	II	II
Kaolin, colloidal	II	II
Knotgrass	II	II
Lactic acid	II	II
Lactose	II	II
Lavender compound, tincture of.	II	II
Linden	II	II
Lipase	II	II
Lysine hydrochloride	II	II
Mannitol	II	II
Mycozyme	II	II
Myrrh, fluid extract of	II	II
Nettle	II	II
Nickel-pectin	II	II
Nux vomica extract	II	II
Orthophosphoric acid	II	II
Papaya, natural	II	II
Pectin	II	II
Peppermint	II	II
Peppermint spirit	II	II
Phenacetin	II	II
Potassium bicarbonate	II	II
Potassium carbonate	II	II
Protease	II	II
Prolase	II	II
Rhubarb fluid extract	II	II
Senna	II	II
Sodium chloride	II	II
Sodium salicylate	II	II
Stem bromelain	II	II
Strawberry	II	II
Strychnine	II	II
Tannic acid	II	II
Trillium	II	II
Woodruff	II	II
(2) Topical antifungal drug products.—(i) Topical antifungal drug products:		
Alcloxa	III	III
Alum, potassium	III	III
Aluminum sulfate	III	III
Amyltricresols, secondary	III	III
Basic fuchsin	III	III
Benzethonium chloride	III	III
Benzoic acid	III	III
Benzoxiquine	III	III
Boric acid	III	III
Camphor	II	II
Candicidin	III	III
Chlorothymol	III	III
Coal tar	II	II
Dichlorophen	III	III
Menthol	II	II
Methylparaben	III	III
Oxyquinoline	III	III
Oxyquinoline sulfate	III	III
Phenol	II	III
Phenolate sodium	II	III
Phenyl salicylate	III	III
Propionic acid	III	III
Propylparaben	III	III
Resorcinol	II	II
Salicylic acid	III	III
Sodium borate	III	III
Sodium caprylate	III	III
Sodium propionate	III	III
Sulfur	III	III
Tannic acid	II	II
Thymol	II	II
Tolindate	II	II
Triacetin	III	III
Zinc caprylate	III	III
Zinc propionate	III	III
(ii) Diaper rash drug products-Any ingredient	N/A	II
(3) External analgesic drug products.—(i) Diaper rash drug products: Any ingredient	N/A	II
(ii) Fever blister and cold sore treatment drug products:		
Allyl isothiocyanate	N/A	III
Aspirin	N/A	III
Bismuth sodium tartrate	N/A	III
Camphor	N/A	III
Capsaicin	N/A	III
Capsicum	N/A	III
Capsicum oleoresin	N/A	III
Chloral hydrate	N/A	II
Chlorobutanol	N/A	III
Cyclomethycaine sulfate	N/A	III
Eucalyptus oil	N/A	III
Eugenol	N/A	III
Glycol salicylate	N/A	III
Hexylresorcinol	N/A	III
Histamine dihydrochloride	N/A	III
Menthol	N/A	III
Methapyrilene hydrochloride	N/A	II
Methyl nicotinate	N/A	III
Methyl salicylate	N/A	III
Pectin	N/A	III
Salicylamide	N/A	III
Strong ammonia solution	N/A	III
Tannic acid	N/A	III
Thymol	N/A	III
Tripelennamine hydrochloride.	N/A	III
Trolamine salicylate	N/A	III
Turpentine oil	N/A	III
Zinc sulfate	N/A	III
(iii) Insect bite and sting drug products:		
Alcohol	II	II
Alcohol, ethoxylated alkyl	II	II
Benzalkonium chloride	II	II
Calamine	II	II
Ergot fluidextract	II	II
Ferric chloride	II	II
Panthenol	N/A	III
Peppermint oil	II	II
Pyrilamine maleate	II	II
Sodium borate	II	II
Trolamine salicylate	III	III
Turpentine oil	II	II
Zinc oxide	II	II
Zirconium oxide	II	II
(iv) Poison ivy, poison oak, and poison sumac drug products:		
Alcohol	N/A	II
Aspirin	N/A	III
Benzethonium chloride	N/A	II
Benzocaine (0.5 to 1.25 percent).	N/A	III
Bithionol	N/A	II
Calamine	N/A	II
Cetalkonium chloride	N/A	II
Chloral hydrate	N/A	II
Chlorobutanol	N/A	III
Chlorpheniramine maleate	N/A	II
Creosote, beechwood	N/A	II
Cyclomethycaine sulfate	N/A	III
Dexpanthenol	N/A	III
Diperodon hydrochloride	N/A	II
Eucalyptus oil	N/A	II
Eugenol	N/A	III
Glycerin	N/A	II
Glycol salicylate	N/A	III
Hectorite	N/A	II
Hexylresorcinol	N/A	II
Hydrogen peroxide	N/A	II
Impatiens biflora tincture	N/A	II
Iron oxide	N/A	II
Isopropyl alcohol	N/A	II
Lanolin	N/A	II
Lead acetate	N/A	II
Merbromin	N/A	II
Mercuric chloride	N/A	II
Methapyrilene hydrochloride	N/A	II
Panthenol	N/A	III
Parethoxycaine hydrochloride.	N/A	II
Phenyltoloxamine dihydrogen citrate.	N/A	II

TABLE II.—INGREDIENTS COVERED BY THIS NOTICE—Continued

Rulemaking and ingredients	Ingredient classification	
	ANPRM	NPRM
Povidone-vinylacetate co-polymers.	N/A	II
Pyrilamine maleate	N/A	II
Salicylamide	N/A	III
Salicylic acid	N/A	II
Simethicone	N/A	II
Sulfur	N/A	II
Tannic acid	N/A	III
Thymol	N/A	III
Trolamine	N/A	II
Turpentine oil	N/A	II
Zirconium oxide	N/A	II
Zyloxin	N/A	II
(4) Internal analgesic drug products:		
Aminobenzoic acid [1]	II	II
Antipyrine	III	III
Aspirin, aluminum	III	III
Calcium salicylate	N/A	II
Codeine	II	II
Codeine phosphate	II	N/A
Codeine sulfate	II	N/A
Iodoantipyrine	II	II
Lysine aspirin	N/A	II
Methapyrilene fumarate [1]	III	II
Phenacetin	II	II
Pheniramine maleate [1]	III	III
Pyrilamine maleate [1]	III	III
Quinine	II	II
Salsalate	III	III
Sodium aminobenzoate [1]	II	II
(5) Orally administered menstrual drug products:		
Alcohol	II	II
Alfalfa leaves	II	II
Aloes	II	II
Asclepias tuberosa	II	II
Asparagus	II	II
Barosma	II	II
Bearberry (extract of uva ursi).	II	II
Bearberry fluidextract (extract of bearberry).	II	II
Blessed thistle (cnicus benedictus).	II	II
Buchu powdered extract (extract of buchu).	II	II
Calcium lactate	II	II
Calcium pantothenate	II	II
Capsicum oleoresin	II	II
Cascara fluidextract, aromatic (extract of cascara).	II	II
Chlorprophenpyridamine maleate.	II	II
Cimicifuga racemosa	II	II
Codeine	II	II
Collinsonia (extract stone root).	II	II
Corn silk	II	II
Couch grass	II	II
Dog grass extract	II	II
Ethyl nitrite	II	II
Ferric chloride	II	II
Ferrous sulfate	II	II
Gentiana lutea (gentian)	II	II
Glycyrrhiza glabra (licorice root).	II	II
Homatropine methylbromide	II	II
Hydrangea, powdered extract (extract of hydrangea).	II	II
Hydrastis canadensis (golden seal).	II	II
Hyoscyamine sulfate	II	II
Juniper oil (oil of juniper)	II	II
Magnesium sulfate	II	II
Methapyrilene hydrochloride	II	II

TABLE II.—INGREDIENTS COVERED BY THIS NOTICE—Continued

Rulemaking and ingredients	Ingredient classification	
	ANPRM	NPRM
Methenamine	II	II
Methylene blue	II	II
Natural estrogenic hormone	II	II
Niacinamide	II	II
Nutmeg oil (oil of nutmeg)	II	II
Oil of erigeron	II	II
Parsley	II	II
Peppermint spirit	II	II
Pepsin, essence	II	II
Phenacetin	II	II
Phenindamine tartrate	II	II
Phenyl salicylate	II	II
Piscidia erythrina	II	II
Pipsissewa	II	II
Potassium acetate	II	II
Potassium nitrate	II	II
Riboflavin	II	II
Saw palmetto	II	II
Senecio aureus	II	II
Sodium benzoate	II	II
Sodium nitrate	II	II
Sucrose	II	II
Sulfurated oils of turpentine	II	II
Taraxacum officinale	II	II
Theobromine sodium salicylate.	III	III
Theophylline	III	III
Thiamine hydrochloride	II	II
Triticum	II	II
Turpentine, venice (venice turpentine).	II	II
Urea	II	II
(6) Pediculicide drug products:		
Benzocaine	II	II
Benzyl alcohol	II	II
Benzyl benzoate	II	II
Chlorophenothane (dichlorodiphenyl trichloroethane).	II	II
Coconut oil soap, aqueous	II	II
Copper oleate	II	II
Docusate sodium	II	II
Formic acid [2]	N/A	N/A
Isobornyl thiocyanoacetate	II	II
Picrotoxin	II	II
Propylene glycol	II	II
Sabadilla alkaloids	II	II
Sulfur, sublimed	II	II
Thiocyanoacetate	II	II
(7) Skin protectant drug products.—(i) Astringent drug products:		
Acetone	II	II
Alcohol	II	II
Alum, ammonium	II	II
Alum, potassium	II	II
Aluminum chlorhydroxy complex.	II	II
Aromatics	II	II
Benzalkonium chloride	II	II
Benzethonium chloride	II	II
Benzocaine	II	II
Benzoic acid	II	II
Boric acid	II	II
Calcium acetate	II	II
Camphor gum	II	II
Clove oil	II	II
Colloidal oatmeal	II	II
Cresol	II	II
Cupric sulfate	II	II
Eucalyptus oil	II	II
Eugenol	II	II
Honey	II	II
Isopropyl alcohol	II	II
Menthol	II	II
Methyl salicylate	II	II
Oxyquinoline sulfate	II	II

TABLE II.—INGREDIENTS COVERED BY THIS NOTICE—Continued

Rulemaking and ingredients	Ingredient classification	
	ANPRM	NPRM
P-t-butyl-m-cresol	II	II
Peppermint oil	II	II
Phenol	II	II
Polyoxyethylene laurate	II	II
Potassium ferrocyanide	II	II
Sage oil	II	II
Silver nitrate	II	II
Sodium borate	II	II
Sodium diacetate	II	II
Talc	II	II
Tannic acid glycerite	II	II
Thymol	II	II
Topical starch	II	II
Zinc chloride	II	II
Zinc oxide	II	II
Zinc phenolsulfonate	II	II
Zinc stearate	II	II
Zinc sulfate	II	II
(ii) Diaper rash drug products:		
Aluminum hydroxide	N/A	III
Cocoa butter	N/A	III
Cysteine hydrochloride	N/A	III
Glycerin	N/A	III
Protein hydrolysate	N/A	III
Racemethionine	N/A	III
Sulfur	N/A	II
Tannic acid	N/A	II
Zinc acetate	N/A	III
Zinc carbonate	N/A	III
(iii) Fever blister and cold sore treatment drug products:		
Bismuth subnitrate	N/A	II
Boric acid	N/A	II
Pyridoxine hydrochloride	N/A	II
Sulfur	N/A	II
Tannic acid	N/A	III
Topical starch	N/A	III
Trolamine	N/A	III
Zinc sulfate	N/A	III
(iv) Insect bite and sting drug products:		
Alcohol	II	II
Alcohol, ethoxylated alkyl	II	II
Ammonia solution, strong	II	II
Ammonium hydroxide	III	III
Benzalkonium chloride	II	II
Camphor	II	II
Ergot fluidextract	II	II
Ferric chloride	II	II
Menthol	II	II
Peppermint oil	II	II
Phenol	II	II
Pyrilamine maleate	II	II
Sodium borate	II	II
Trolamine	III	III
Turpentine oil	II	II
Zirconium oxide	II	II
(v) Poison ivy, poison oak, and poison sumac drug products:		
Alcohol	N/A	II
Anion and cation exchange resins buffered.	III	III
Benzethonium chloride	N/A	II
Benzocaine	N/A	II
Benzyl alcohol	N/A	II
Bismuth subnitrate	N/A	II
Bithionol	N/A	II
Boric acid	N/A	II
Camphor	N/A	II
Cetalkonium chloride	N/A	II
Chloral hydrate	N/A	II
Chlorpheniramine maleate	N/A	II
Creosote	N/A	II
Diperodon hydrochloride	N/A	II
Diphenhydramine hydrochloride.	N/A	II

TABLE II.—INGREDIENTS COVERED BY THIS NOTICE—Continued

Rulemaking and ingredients	Ingredient classification	
	ANPRM	NPRM
Eucalyptus oil	N/A	II
Ferric chloride	II	II
Glycerin	N/A	II
Hectorite	N/A	II
Hydrogen peroxide	N/A	II
Impatiens biflora tincture	N/A	II
Iron oxide	N/A	II
Isopropyl alcohol	N/A	II
Lanolin	N/A	II
Lead acetate	N/A	II
Lidocaine	N/A	II
Menthol	N/A	II
Merbromin	N/A	II
Mercuric chloride	N/A	II
Panthenol	N/A	II
Parethoxycaine hydrochloride.	N/A	II
Phenol	N/A	II
Phenyltoloxamine dihydrogen citrate.	N/A	II
Povidone-vinylacetate copolymers.	N/A	II
Salicylic acid	N/A	II
Simethicone	N/A	II
Tannic acid	N/A	II
Topical starch	N/A	III
Trolamine	N/A	III
Turpentine oil	N/A	II
Zirconium oxide	N/A	II
Zyloxin	N/A	II

N/A Means that the ingredient was either not classified by the Panel or was not included in the indicated (ANPRM/NPRM) document.

[1] Ingredient used as an analgesic-antipyretic adjuvant.

[2] This ingredient was not submitted to or previously classified in the OTC drug review, but has been observed in a marketed product.

II. The Agency's Tentative Conclusions on Certain OTC Drug Category II and III 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 above as being generally recognized as safe and effective for the OTC drug uses specified in Table II. Based on the agency's procedural regulations (§ 330.10(a)(7)(ii)), the agency has determined that these ingredients should be deemed not generally recognized as safe and effective for OTC use before a final monograph for each respective drug category is established. Accordingly, any drug product containing any of these 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 ingredients in OTC drug products. (See 21 CFR 10.30.) Any OTC drug product containing any of the above ingredients and labeled for the use identified above initially introduced or initially delivered for introduction into interstate commerce after the effective date of a final rule in this proceeding to remove these Category II and III ingredients from the market and that is not the subject of an approved application will be in violation of sections 502 and 505 of the act and, therefore, subject to regulatory action. Further, any OTC drug product subject to the final rule that is repackaged or relabeled after the effective date of the rule would be required to 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.

The agency has examined the economic consequences of this proposed rulemaking. The agency invited public comment in the notices of proposed rulemaking listed in Table I regarding any impact that those rulemakings would have on drug products containing the above specified OTC drug ingredients. No comments on economic impacts were received. Moreover, manufacturers of products containing these ingredients have not provided any substantive data to support their continued marketing. Accordingly, the agency concludes that there is no basis for the continued marketing of these ingredients for the indications listed in Table II. Further, in most cases, there are proposed rulemaking ingredients which manufacturers can use to reformulate affected products. In many instances, manufacturers have already reformulated their products to include monograph ingredients. As a result of this proposal, manufacturers may need to reformulate some products prior to promulgation of the applicable final monograph. However, there will be no additional costs because reformulation will 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 have been found to be generally recognized as safe and effective without incurring additional expense of clinical testing for these ingredients. Based on the above, the agency certifies that this proposed rule, if implemented, will not have a significant economic impact on a substantial number of small entities.

Any comments on the agency's initial determination of the economic consequences of this proposed rulemaking should be submitted by October 26, 1992. Such comments should be submitted to the Dockets Management Branch (address above) and identified with the docket number found in brackets in the heading of this document and not to the docket numbers appearing in Table I. The agency will evaluate any comments and supporting data that are received and will reassess the economic impact of this rulemaking in the preamble to the final rule.

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.

Interested persons may, on or before October 26, 1992, submit to the Dockets Management Branch (address above) written comments, objections, or requests for oral hearing before the Commissioner on the proposed rulemaking. A request for an oral hearing must specify points to be covered and time requested. Written comments on the agency's economic impact determination may be submitted on or before October 26, 1992. Three copies of all comments, objections, and requests are to be submitted, except that individuals may submit one copy. Comments, objections, and requests are to be identified with the appropriate docket number found in brackets in the heading of this document and not the docket numbers appearing in Table I, and may be accompanied by a supporting memorandum or brief. Comments, objections, and requests may be seen in the office above between 9 a.m. and 4 p.m., Monday through Friday. Any scheduled oral hearing will be announced in the **Federal Register**.

List of Subjects in 21 CFR Part 310

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

Therefore, under the Federal Food, Drug, and Cosmetic Act and under authority delegated to the Commissioner of Food and Drugs, it is proposed that 21 CFR part 310 be amended as follows:

PART 310—NEW DRUGS

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

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

2. Section 310.545 is amended by redesignating paragraphs (a)(8) and (a)(18) as (a)(8)(i) and (a)(18)(i), respectively; by revising the heading of new paragraphs (a)(8)(i) and (a)(18)(i), (d) introductory text, and (d)(1); and by adding new (a)(8) heading and paragraphs (a)(8)(ii), (a)(10)(iv) through (a)(10)(vii), and (a)(18) heading, paragraphs (a)(18)(ii) through (a)(18)(vi), (a)(21)(i) and (a)(21)(ii), (a)(22) through (a)(24), and (d)(4) to read as follows:

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

(a) * * *

(8) *Digestive aid drug products*—(i) *Approved as of May 7, 1991.* * * *

(ii) *Approved as of February 26, 1993.*

Alcohol
Aluminum hydroxide
Amylase
Anise seed
Aromatic powder
Asafetida
Aspergillus oryza enzymes
Bacillus acidophilus
Bean
Belladonna alkaloids
Belladonna leaves, powdered extract
Betaine hydrochloride
Bismuth subcarbonate
Bismuth subgallate
Black radish powder
Blessed thistle (cnicus benedictus)
Buckthorn
Calcium gluconate
Capsicum
Capsicum, fluid extract of
Carbon
Cascara sagrada extract
Catechu, tincture
Catnip
Chamomile flowers
Charcoal, wood
Chloroform
Cinnamon oil
Cinnamon tincture
Citrus pectin
Diastase
Diastase malt
Dog grass
Elecampane
Ether
Fennel acid
Galega
Ginger
Glycine
Golden seal (hydrastis canadensis)
Hectorite
Horsetail
Huckleberry
Hydrastis fluid extract
Hydrochloric acid
Iodine
Iron ox bile
Johnswort
Juniper
Kaolin, colloidal
Knotgrass
Lactic acid
Lactose
Lavender compound, tincture of
Linden
Lipase
Lysine hydrochloride
Mannitol
Mycozyme
Myrrh, fluid extract of
Nettle
Nickel-pectin
Nux vomica extract
Orthophosphoric acid
Papaya, natural
Pectin
Peppermint
Peppermint spirit
Phenacetin
Potassium bicarbonate
Potassium carbonate
Protease
Prolase
Rhubarb fluid extract
Senna
Sodium chloride
Sodium salicylate
Stem bromelain
Strawberry
Strychnine
Tannic acid
Trillium
Woodruff

* * * * *

(10) * * *

(iv) *Diaper rash drug products.* Any ingredient(s) labeled with claims or directions for use in the treatment and/or prevention of diaper rash.

(v) *Fever blister and cold sore treatment drug products.*

Allyl isothiocyanate
Asprin
Bismuth sodium tartrate
Camphor
Capsaicin
Capsicum oleoresin
Chloral hydrate
Chlorobutanol
Cyclomethycaine sulfate
Eucalyptus oil
Eugenol
Glycol salicylate
Hexylresorcinol
Histamine dihydrochloride
Menthol
Methapyrilene hydrochloride
Methyl nicotinate
Methyl salicylate
Pectin
Salicylamide
Strong ammonia solution
Tannic acid
Thymol
Tripelennamine hydrochloride
Trolamine salicylate
Turpentine oil
Zinc sulfate

(vi) *Insect bite and sting drug products.*

Alcohol
Alcohol, ethoxylated alkyl
Benzalkonium chloride
Calamine
Ergot fluidextract
Ferric chloride
Panthenol
Peppermint oil
Pyrilamine maleate
Sodium borate
Trolamine salicylate
Turpentine oil
Zinc oxide
Zirconium oxide

(vii) *Poison ivy, poison oak, and poison sumac drug products.*

Alcohol
Aspirin
Benzethonium chloride
Benzocaine (0.5 to 1.25 percent)
Bithionol
Calamine
Cetalkonium chloride
Chloral hydrate
Chlorobutanol
Chlorpheniramine maleate
Creosote, beechwood
Cyclomethycaine sulfate
Dexpanthenol
Diperodon hydrochloride
Eucalyptus oil
Eugenol
Glycerin
Glycol salicylate
Hectorite

Hexylrosorcinol
Hydrogen peroxide
Impatiens biflora tincture
Iron oxide
Isopropyl alcohol
Lanolin
Lead acetate
Merbromin
Mercuric chloride
Methapyrilene hydrochloride
Panthenol
Parethoxycaine hydrochloride
Phenyltoloxamine dihydrogen citrate
Povidone-vinylacetate copolymers
Pyrilamine maleateSalicylamide
Salicylic acid
Simethicone
Sulfur
Tannic acid
Thymol
Trolamine salicylate
Turpentine oil
Zirconicum oxide
Zyloxin

* * * * *

(18) *Skin protectant drug products*—(i) *Ingredients.* * * *

(ii) *Astringent drug products.*

Acetone
Alcohol
Alum, ammonium
Alum, potassium
Aluminum chlorhydroxy complex
Aromatics
Benzalkonium chloride
Benzethonium chloride
Benzocaine
Benzoic acid
Boric acid
Calcium acetate
Camphor gum
Clove oil
Colloidal oatmeal
Cresol
Cupric sulfate
Eucalyptus oil
Eugenol
Honey
Isopropyl alcohol
Menthol
Methyl salicylate
Oxyquinoline sulfate
P-t-butyl-m-cresol
Peppermint oil
Phenol
Polyoxytheylene laurate
Potassium ferrocyanide
Sage oil
Silver nitrate
Sodium borate
Sodium diacetate
Talc
Tannic acid glycerite
Thymol
Topical starch
Zinc chloride
Zinc oxide
Zinc phenolsulfonate
Zinc stearate
Zinc sulfate

(iii) *Diaper rash drug products.*

Aluminum hydroxide
Cocoa butter
Cysteine hydrochloride
Glycerin
Protein hydrolysate
Racemethionine
Sulfur
Tannic acid
Zinc acetate
Zinc carbonate

(iv) *Fever blister and cold sore treatment drug products.*

Bismuth subnitrate
Boric acid
Pyridoxide hydrochloride
Sulfur
Tannic acid
Topical starch
Trolamine
Zinc sulfate

(v) *Insect bite and sting drug products.*

Alcohol
Alcohol, ethoxylated alkyl
Ammonia solution, strong
Ammonium hydroxide
Benzalkonium chloride
Camphor
Ergot fluidextract
Ferric chloride
Menthol
Peppermint oil
Phenol
Pyrilamine maleate
Sodium borate
Trolamine
Turpentine oil
Zirconium oxide

(vi) *Poison ivy, poison oak, and poison sumac drug products.*

Alcohol
Anion and cation exchange resins buffered
Benzethonium chloride
Benzocaine
Benzyl alcohol
Bismuth subnitrate
Bithionol
Boric acid
Camphor
Cetalkonium chloride
Chloral hydrate
Chlorpheniramine maleate
Creosote
Diperodon hydrochloride
Diphenhydramine hydrochloride
Eucalyptus oil
Ferric chloride
Glycerin
Hectorite
Hydrogen peroxide
Impatiens biflora tincture
Iron oxide
Isopropyl alcohol
Lanolin
Lead acetate
Lidocaine
Menthol
Merbromin
Mercuric chloride
Panthenol
Parethoxycaine hydrochloride
Phenol
Phenyltoloxamine dihydrogen citrate
Povidone-vinylacetate copolymers
Salicylic acid
Simethicone
Tannic acid
Topical starch
Trolamine
Turpentine oil
Zirconium oxide
Zyloxin

* * * * *

(21) *Topical antifungal drug products.*

(i) *Ingredients.*

Alcloxa
Alum, potassium
Aluminum sulfate
Amyltricresols, secondary
Basic fuchsin
Benzethonium chloride
Benzoic acid
Benzoxiquine
Boric acid
Camphor
Candicidin
Chlorothymol
Coal tar
Dichlorophen
Menthol
Methylparaben
Oxyquinoline
Oxyquinoline sulfate
Phenol
Phenolate sodium
Phenyl salicylate
Propionic acid
Propylparaben
Resorcinol
Salicylic acid
Sodium borate
Sodium caprylate
Sodium propionate
Sulfur
Tannic acid
Thymol
Tolindate
Triacetin
Zinc caprylate
Zinc propionate

(ii) *Diaper rash drug products.* Any ingredient(s) labeled with claims or directions for use in the treatment and/or prevention of diaper rash.

(22) *Internal analgesic drug products.*

Aminobenzoic acid
Antipyrine
Aspirin, aluminum
Calcium salicylate
Codeine
Codeine phosphate

Codeine sulfate
Iodoantipyrine
Lysine aspirin
Methapyrilene fumarate
Phenacetin
Pheniramine maleate
Pyrilamine maleate
Quinine
Salsalate
Sodium aminobenzoate

(23) *Orally administered menstrual drug products.*

Alcohol
Alfalfa leaves
Aloes
Asclepias tuberosa
Asparagus
Barosma
Bearberry (extract of uva ursi)
Bearberry fluidextract (extract of bearberry)
Blessed thistle (cnicus benedictus)
Buchu powdered extract (extract of buchu)
Calcium lactate
Calcium pantothenate
Capsicum oleorisin
Cascara fluidextract, aromatic (extract of cascara)
Chlorprophenpyridamine maleate
Cimicifuga racemosa
Codeine
Collinsonia (extract stone root)
Corn silk
Couch grass
Dog grass extract
Ethyl nitrite
Ferric chloride
Ferrous sulfate
Gentiana lutea (gentian)
Glycyrrhiza (licorice)
Homatropine methylbromide
Hydrangea, powdered extract (extract of hydrangea)
Hydrastis canadensis
Hyoscyamine sulfate
Juniper oil (oil of juniper)
Magnesium sulfate
Methapyrilene hydrochloride
Methenamine
Methylene blue
Natural estrogenic hormone
Niacinamide
Nutmeg oil (oil of nutmeg)
Oil of erigeron
Parsley
Peppermint spirit
Pepsin, essence
Phenacetin
Phenindamine tartrate
Phenyl salicylate
Piscidia erythrina
Pipsissewa
Potassium acetate
Potassium nitrate
Riboflavin
Saw palmetto
Senecio aureus
Sodium benzoate
Sodium nitrate
Sucrose
Sulferated oils of turpentine
Taraxacum officinale
Theobromine sodium salicylate
Theophylline
Thiamine hydrochloride
Triticum
Turpentine, venice
Urea

(24) *Pediculicide drug products.*

Benzocaine
Benzyl alcohol
Benzyl benzoate
Chlorophenothane (Dichlorodiphenyl trichloroethane)
Coconut oil soap, aqueous
Copper oleate
Docusate sodium
Formic acid
Isobornyl thiocyanoacetate
Picrotoxin
Propylene glycol
Sabadilla alkaloids
Sulfur, sublimed
Thiocyanoacetate

* * * * *

(d) Any OTC drug product that is not in compliance with this section is subject to regulatory action if initially introduced or initially delivered for introduction into interstate commerce after the dates specified in paragraphs (d)(1) through (d)(4) of this section.

(1) May 7, 1991, for products subject to paragraphs (a)(1) through (a)(8)(i), (a)(9) through (a)(10)(iii), (a)(11) through (a)(18)(i), and (a)(19) of this section.

* * * * *

(4) February 26, 1993, for products subject to paragraphs (a)(8)(ii), (a)(10)(iv) through (a)(10)(vii), (a)(18)(ii) through (a)(18)(vi), (a)(21)(i) and (a)(21)(ii), and (a)(22) through (a)(24) of this section.

Dated: August 19, 1992.

Michael R. Taylor,

Deputy Commissioner for Policy.

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