DEPARTMENT OF HEALTH AND HUMAN SERVICES

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Food and Drug Administration

[Docket No. 2003N–0539]

Over-the-Counter Drug Products; Safety and Efficacy Review

AGENCY: Food and Drug Administration, HHS

ACTION: Request for data and information.

SUMMARY: The Food and Drug Administration (FDA) is announcing a call for data for certain categories of ingredients in over-the-counter (OTC) drug products that are eligible for the original OTC drug review but have not been reviewed by FDA to date. FDA will review the submitted data and information as part of its ongoing review of OTC drug products to determine whether these ingredients and products are generally recognized as safe and effective (GRAS/E) for their labeled uses. This document also requests the identification of other categories of OTC drug products that were in the marketplace when the OTC drug review began on May 11, 1972, or that were marketed before December 4, 1975, and describes FDA's general regulatory policy governing the marketing of these OTC drug products during the pendency of this review.

DATES: Submit data, information, and general comments by [*insert date 180 days after date of publication in the* **Federal Register**].

ADDRESSES: Submit data and information directly to the Division of OTC Drug Products (HFD–560), Center for Drug Evaluation and Research, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857. Submit general comments in writing to the Division of Dockets Management (HFA–305), 5630

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Fishers Lane, rm. 1061, Rockville, MD 20852 or electronically to *http://www.fda.gov/dockets/ecomments.*

FOR FURTHER INFORMATION CONTACT: Michael T. Benson 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 1972, FDA established the OTC drug review to evaluate currently marketed OTC drug products. The final regulations in part 330 (21 CFR part 330) providing for the OTC drug review under 21 CFR 130.301 (recodified as § 330.10) were published and made effective in the **Federal Register** of May 11, 1972 (37 FR 9464). Since that time, FDA has published various calls for data inviting interested parties to submit data and information for the advisory review panels to review.[1] During the course of the OTC drug review, advisory review panels reviewed many of the categories of OTC drug products included in prior call-for-data notices but did not review every category because of resource limitations.[2] Table 1 of this document lists the categories of OTC drug products reviewed by all 17 panels and FDA and several categories of products that were reviewed by FDA only.

TABLE 1.—CATEGORIES OF OTC DRUG PRODUCTS REVIEWED BY 17 PANELS AND/OR FDA

AcneAlcohol

[1]See 38 FR 31696, November 16, 1973, and 40 FR 38179, August 27, 1975.

[2]FDA also identified several categories of marketed OTC drug products that were not reviewed by the advisory panels and publish subsequent call-for-data notices for those product categories. In the **Federal Register** of December 5, 1989 (54 FR 50240), FDA published a request for data and information on ingredients in eyewash drug products used for emergency first aid treatment of chemical burns of the eyes. FDA publshed a proposed rule for those products in the **Federal Register** of September 19, 1990 (55 FR 38560), FDA published a request for data and information on ingredients contained in products bearing antiplaque and antiplaque-related claims. The Dental Products Panel completed its review of the data and information that were submitted, and FDA published the panel's report in the **Federal Register** of May 29, 2003 (68 FR 32232).

TABLE 1.—CATEGORIES OF OTC DRUG PRODUCTS REVIEWED BY 17 PANELS AND/OR FDA—Continued

Anorectal
Antacid
Anthelmintic
Anticaries
Antidiarrheal
Antiemetic
Antiflatulent
Antifungal:
  Diaper Rash
  Nails and Scalp
Antimicrobial:
  Alcohols (topical)
  Antiseptics (First aid)
  Antiseptics (Health Care)
  Diaper Rash
  Mercurials
Antiperspirant
Aphrodisiac
Benign Prostatic Hypertrophy
Boil Treatment
Camphorated Oil
Category II/III Ingredients (Phase I)
Category II/III Ingredients (Phase II)
Category II/III Ingredients (Additional)
Cholecystokinetic
Corn/Callus Remover
Cold/Cough:
  Anticholinergic
  Antihistamine
  Antitussive
  Bronchodilator
  Expectorant
  Nasal Decongestant
Dandruff/Seborrhea/Psoriasis
Daytime Sedative
Deodorant (Internal)
Digestive Aid
Exocrine Pancreatic Insufficiency
External Analgesic:
  Diaper Rash
  Fever Blister/Cold Sore
  Insect Bites/Stings
  Male Genital Desensitizer
  Poison Ivy/Oak/Sumac
Fever Blister/Cold Sore (Internal)
Hair Grower/Loss
Hexachlorophene
Hormone (topical)
Hypo/Hyperphosphatemia
Ingrown Toenail Relief
Insect Repellent (Internal)
Internal Analgesic:
  Leg Muscle Cramps
  Malaria
  Overindulgence
Laxative
Menstrual
Nailbiting/Thumbsucking Deterrent
Nighttime Sleep-aid
Ophthalmic
Oral Health Care:
  Antiseptic
  Non-Antimicrobial
  Oral Discomfort (Relief)
  Oral Mucosal Injury
  Oral Wound Healing
  Plaque
Otic:
  Drying Water-Clogged Ears
  Earwax Removal
  Swimmer's Ear
Overindulgence Remedies:
  Prevent Inebriation
Pediculicide
Poison Treatment:
  Acute Toxic Ingestion Treatment
  Emetic
Salicylanilides (Tribromsalan)
Silver
Skin Bleaching
Skin Protectant:

TABLE 1.—CATEGORIES OF OTC DRUG PRODUCTS REVIEWED BY 17 PANELS AND/OR FDA—Continued

Astringent
Diaper Rash
Fever Blister/Cold Sore
Insect Bites/Stings
Poison Ivy/Oak/Sumac
Smoking Deterrent
Stimulant
Stomach Acidifier
Sunscreen
Sweet Spirits of Nitre
Vaginal Contraceptive
Vaginal Drug Products
Vitamin/Mineral
Wart Remover
Weight Control
Zirconium (Aerosol)

II. The Current Request for Data and Information

To complete the OTC drug review, FDA is publishing this call-for-data notice on the following categories of ingredients: (1) Nasal moisturizer drug products, (2) urinary analgesic/antiseptic drug products, (3) urinary acidifiers and alkalinizers, (4) aloe vera and urea, (5) wrinkle remover products, and (6) lubricants and vaginal moisturizers. The categories of OTC drugs in this notice include some of the categories from the 1973 and 1975 notices that were not reviewed and several other categories that the agency has identified that were never reviewed. These include urinary analgesics/antiseptics and saline nasal products. Interested parties who identify other categories of OTC drug products that were in the marketplace when the OTC drug review began on May 11, 1972, or that were marketed before December 4, 1975 (see § 330.13), should submit comments regarding this document to the agency about those categories of OTC drug products, including the active ingredients in the products and the uses for which the products were marketed. Product labels should be provided if available.

A. Nasal Moisturizer Drug Products

The agency considers nasal moisturizer products[3] to be drugs when they contain the following or similar ingredients: Sodium chloride, normal saline, buffered isotonic saline solution, saline phosphate buffer solution, glycerin. A number of these nasal moisturizer products have been marketed for several years with various labeling claims. Such claims include the following statements:

•"provides soothing moisture to dry, inflamed nasal membranes due to colds, allergies, low humidity, and other minor nasal irritations"

•"restores vital moisture to provide prompt relief for dry, crusted, and inflamed nasal membranes due to chronic sinusitis, colds, low humidity, overuse of nasal decongestant drops and sprays, allergies, minor nose bleeds, and other minor nasal irritations"

•"use for dry nasal membranes caused by chronic sinusitis, allergy, asthma, dry air, oxygen therapy"

•"rhinitis medicamentosa, rhinitis sicca, and atrophic rhinitis for patients 'hooked on nose drops' and glaucoma patients on diuretics having dry nasal capillaries"

•"a nasal moisturizer formulated to be physiologically compatible with nasal membranes, providing soothing relief for clogged nasal passages without stinging or burning"

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[3]In its report on OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products (published in the **Federal Register** of September 9, 1976 (41 FR 38312)), the panel that reviewed these products classified saline phosphate buffer solution as an inactive ingredient or pharmaceutical necessity, and did not classify it as a nasal moisturizer. The panel did not review and evaluate products used as nasal moisturizers, and these products were not reviewed and evaluated in the various tentative final and final monographs under the rulemaking for OTC cold, cough, allergy, bronchodilator, and antiasthmatic drug products.

•"restores moisture to relieve dry, inflamed nasal membranes due to low humidity, colds, allergies, and overuse of nasal decongestants".

FDA currently desires additional data on which to make a determination as to the safety, effectiveness, and labeling of these products. There may be other labeling statements or formulations of the products that are marketed as OTC nasal moisturizers. FDA considers many of these claims to be drug claims and believes these products should be regulated under the monograph for OTC cough-cold or miscellaneous internal drug products. Therefore, FDA requests that interested persons who have data and information on the safety and effectiveness of nasal moisturizer products submit them to FDA at this time.

B. Urinary Analgesic/Antiseptic Drug Products

FDA is also aware that products marketed as urinary analgesics/antiseptics and products for too frequent, burning, and painful urination have been marketed for a number of years, but have not yet been evaluated as part of the OTC drug review.[4] Other products marketed for these uses for a number of years contain methylene blue and phenazopyridine hydrochloride (HCl).

Phenazopyridine HCl has had a dual prescription/OTC marketing status based on the ingredient's extensive marketing history in the United States that predates the 1951 Durham-Humphrey Amendments to the Federal Food, Drug, and Cosmetic Act (the act). FDA reviewed phenazopyridine HCl/sulfonamide combination products under the Drug Efficacy Study Implementation (DESI 12056) for the treatment of urinary tract infections caused by a sulfonamide-susceptible organism when relief of symptoms of pain, burning, or urgency is needed. None of the single-entity phenazopyridine HCl drugs marketed at

[4]A product containing methenamine, sodium salicylate, salicylamide, and benzoic acid was submitted in response to the 1973 and 1975 call-for-data notices mentioned previously, but has not been reviewed to date. This submission is out-of-date and needs to be updated before the agency begins its review of these products.

that time or now have been the subject of an approved new drug application (NDA).

In the **Federal Register** of July 29, 1983 (48 FR 34516), FDA published a DESI notice containing conditions for approval and marketing of phenazopyridine-containing drug products (single entities or fixed combinations). The notice announced certain required labeling statements for phenazopyridine-containing drug products indicated for use in relieving symptoms associated with a urinary tract infection, and certain required labeling for all phenazopyridine-containing drug products. FDA recommended the following labeling requirements for phenazopyridine-containing drug products (single entities or fixed combinations) for use in the treatment of urinary tract infections:

1. The following information shall be disclosed in the INDICATION section (adapted to the labeling of particular drug products): Treatment of a urinary tract infection with phenazopyridine HCl or a combination drug product containing phenazopyridine HCl should not exceed 2 days because there is lack of evidence that the combined administration of phenazopyridine HCl and an antibacterial provides greater benefit than administration of the antibacterial alone after 2 days.

2. The part of the INDICATION section pertaining to the use of the product in urinary tract infections shall also refer to the DOSAGE and ADMINISTRATION section.

3. In its dosage and dosing interval recommendations pertaining to the use of the product in urinary tract infections, the DOSAGE and ADMINISTRATION section shall show that the product is only indicated for up to 2 days (the effect of phenazopyridine HCl should not be relied upon after 48 hours).

The DESI notice also contained the following labeling requirement for all drug products containing phenazopyridine:

The following statement shall be included in the CARCENOGENESIS subsection of the PRECAUTION section of the labeling:

Long-term administration of phenazopyridine hydrochloride has induced neoplasia in rats (large intestine) and mice (liver). Although no association between phenazopyridine hydrochloride and human neoplasia has been reported, adequate epidemiological studies along these lines have not been conducted.

This information came from a National Cancer Institute technical report (Ref. 1). FDA is not aware of any epidemiological studies that have been done since the report was published in 1978.

The 1983 DESI notice states that the product considered (Azo Gantanol) contained 500 milligrams (mg) of sulfamethoxazole (antibacterial component) and 100 mg of phenazopyridine HCl (analgesic component) per tablet, and this combination is effective only for the first 48-hour treatment period (four tablets initially followed by two tablets every 12 hours, with the last dose administered at 36 hours). There is no evidence that the phenazopyridine HCl component has a beneficial effect on symptoms beyond 48 hours. Therefore, after initial treatment with the combination product, further treatment should be continued only with the sulfonamide.

The way the labeling information appeared in the notice indicated that 200 mg of phenazopyridine was the prescription dose. Products containing lesser amounts (e.g., 190 or 195 mg) have been marketed OTC. The recommended dosage is three times a day after meals. OTC drug products containing phenazopyridine HCl as a urinary analgesic are usually labeled: "Can be used up to 3 times daily for 2 days maximum." One product surveyed

(Ref. 2) does not contain the required carcinogenesis statement on the outer package labeling but does have the statement in a package insert included inside the package.

FDA issued a Compliance Policy Guide on October 1, 1980 (Ref. 3), revised on May 22, 1987 (Ref. 3), that addressed urinary tract preparations containing phenazopyridine HCl. FDA advised that it was not taking regulatory action against products containing this ingredient and lackingand lacking a prescription legend or full-disclosure labeling [based on their deferral to the OTC drug review].

FDA has a number of questions and issues that it plans to consider when it evaluates phenazopyridine HCl for urinary tract analgesic/antiseptic use as part of this review.

1. Is this condition appropriate for self medication?

2. If the answer to the first question is yes, should the product labeling mention the possible need for treatment with an antibacterial drug also?

3. Is there a valid basis for having single-ingredient prescription products with a 200 mg dosage and OTC products with a 190 to 195 mg dosage? What data support these dosages?

4. Have any epidemiological studies been done since 1978 that address the neoplasia findings in the National Cancer Institute technical report (Ref. 1)?

5. Are the neoplasia findings of sufficient concern to restrict this drug to prescription status?

6. Do consumers adequately understand the required carcinogenesis labeling statement? If the answer is no, how should this statement be revised?

7. Should the carcinogenesis labeling statement be required to appear on the outer package labeling, or is it adequate that it appear only in a package insert?

8. Provide updated safety data both from the literature and from adverse event reports for the last 20 years, especially those adverse events reported to companies that market these products.

FDA invites parties interested in the OTC status of this ingredient to submit their answers to these questions and any supporting data to the Division of Dockets Management as comments to this notice so that this information will be publicly available when FDA reviews this ingredient. Adverse event reports should not include names or telephone numbers.

C. Urinary Acidifiers and Alkalinizers

FDA is also aware of OTC drug products that have been marketed as urinary acidifiers and urinary alkalinizers. Ammonium chloride and ascorbic acid have been used as OTC urinary acidifiers, and sodium bicarbonate has been used as an OTC urinary alkalinizer. These products have not been included in any previous call-for-data notices as part of the OTC drug review. Therefore, at this time FDA invites interested persons to submit data or information on these and any other ingredients for use as OTC urinary acidifiers and alkalinizers.

D. Aloe Vera and Urea

Aloe vera has been present in a variety of OTC drug products. It has been listed as both an active and inactive ingredient. It has been marketed as a skin remedy for minor cuts, burns, abrasions, and for relief of minor irritations of the vagina. The Advisory Review Panel on OTC Contraceptives and Other Vaginal Drug Products (Vaginal Drug Products Panel) placed stabilized aloe

vera in Category III (for effectiveness) for the relief of minor irritations of the vagina (advance notice of proposed rulemaking (ANPRM), 48 FR 46694 at 46711 to 46712, October 13, 1983). The panel mentioned that treatment of minor burns, insect bites, and other conditions in which a wet dressing of aloe vera is used has been widely reported and handed down from generation to generation. FDA withdrew this ANPRM in the **Federal Register** of February 3, 1994 (59 FR 5226), because recommended labeling indications and ingredients used for minor irritation, itching, or soreness are not unique to the vaginal area and are already being considered in other OTC drug rulemakings (e.g., antifungal, antimicrobial, and external analgesic). Therefore, FDA planned to consider the ingredients and indications from the vaginal drug products ANPRM in those other rulemakings, as appropriate. However, no submissions for aloe vera were made to the other rulemakings. Because there may not have been an adequate opportunity for interested parties to submit data and information on aloe vera to those rulemakings, FDA invites interested parties to submit any available data and information at this time before it finalizes the monographs for OTC topical antimicrobial and external analgesic drug products. The monograph for OTC topical antifungal drug products is finalized (21 CFR part 333, subpart C), so any interested parties should submit any data and information on aloe vera for this use as a petition to amend the final monograph.

Urea has been marketed as an antipruritic and keratolytic in a number of topical products, with claims that range from "drug" (relieves itching) to "cosmetic" (for total body dry skin care, soften dry rough skin). Several submissions on products containing urea were made to the Advisory Review Panel on OTC Miscellaneous External Drug Products, but that panel did not

complete its review of those submissions before it was disbanded. The submissions need to be updated for FDA to consider them at this time. No data or information on urea have been submitted to the rulemaking for OTC external analgesic drug products. At this time, FDA invites any interested parties to submit data or information on the use of urea as an external analgesic drug product or for any other OTC drug use.

E. Wrinkle Remover Products

Whether a wrinkle remover product should be regulated as a drug or a cosmetic depends on the claims the manufacturer makes for the product. The regulation of cosmetics is covered in 21 CFR part 700. Manufacturers of these products should examine their labeling for these products and to determine if the products products should be submitted to the OTC drug review for evaluation. Manufacturers should determine if the ingredients in those products affect the structure of the skin in some physiological way and, thus, should be submitted for review as drug ingredients section (see section 201(g)(1)(C) of the act (21 U.S.C. 321(g)(1)(C)). For example, some products marketed since 1971 contain alpha hydroxy acids and beta hydroxy acids. These ingredients are included in this request for data and information.

F. Lubricants and Vaginal Moisturizers

The Vaginal Drug Products Panel reviewed OTC drug products for a number of vaginal uses (48 FR 46694). However, those uses did not include vaginal lubricant or moisturizer. A number of products are marketed as a lubricant, personal lubricant, or lubricating jelly. These products have uses that include: "For personal lubrication when vaginal dryness causes discomfort," "acts as a moisturizer for vaginal dryness," "enhances the comfort and ease of intimate activity," and "enhances sexual pleasure by adding to the body's

natural lubrication." Other products are marketed as lubricating spermicides [lubricant plus nonoxynol-9] or as a lubricant with nonoxynol-9. These products have claims that state "spermicide, nonoxynol-9, plus safe water-soluble personal lubrication, feels natural and helps enhance sexual pleasure, lubricating protection against unplanned pregnancy," and "enhances sexual pleasure by adding to the body's natural lubrication, not a contraceptive; however, because it may kill some sperm, it should not be used if pregnancy is desired." FDA considers claims related to relief of discomfort and claims related to the comfort and ease of sexual activity to be drug claims as they relate to the mitigation or treatment of disease (section 201(g)(1)(B) of the act) or use of a product to affect the structure or function of the body (section 201(g)(1)(C) of the act).

Some of these lubricant products also have claims such as: "For [or eases] insertion of rectal thermometers, enemas, douches, and similar types of nozzles, [and tampons and condoms]" and "widely used in gynecological and hospital procedures." Such claims make these products medical devices, and FDA has regulated them as such since 1976. FDA regulations in 21 CFR part 880 subpart G list products that are general hospital and personal use miscellaneous devices. The regulation in 21 CFR 880.6375 entitled "patient lubricant" states: "A patient lubricant is a device intended for medical purposes that is used to lubricate a body orifice to facilitate entry of a diagnostic or therapeutic device." Claims related to insertion of or facilitating use of rectal thermometers, enemas, douches, tampons, and condoms are considered device claims and are not included as part of this call for data. As these products with device claims can also have drug claims as discussed

previously, FDA invites the submission of data to support the drug claims as part of this call for data.

Products marketed as a vaginal moisturizer have claims such as "replenishes your natural moisture for days at a time," "with regular use, provides continuous vaginal moisture for most women," and "safe immediate relief of vaginal dryness." FDA also considers these to be drug claims because they discuss affecting the structure or function of the body and, in some cases, may relate to the mitigation of a disease. Thus, they are also part of this call for data. FDA does not consider these uses of lubricants or vaginal moisturizers to be cosmetic claims because they do not relate to "cleansing, beautifying, promoting attractiveness, or altering the appearance" (see section 201(i) of the act).

G. Categories of Unreviewed Drug Products and Ingredients

The categories of unreviewed drug products listed in the following paragraphs are included in this call for data. The ingredients listed under each category heading are those that FDA has identified as possibly being in these products. This list is not intended to be all-inclusive. Manufacturers of drug products in categories not previously reviewed or that contain ingredients not listed herein should submit appropriate information to FDA.

Ammonia as a reflex stimulant
  Ammonia inhalants, aromatic spirits of ammonia
Bed-wetting deterrents
  Belladonna
Blemish remedies (excluding topical acne active ingredients in 21 CFR 310.545(a)(1) and 333.310)
  Allantoin, aloe vera gel, calamine, ethyl alcohol, eugenol, menthol, oil of eucalyptus, oil of peppermint, propylene glycol, sodium alkylarylpolyether sulfonate, titanium dioxide, triclocarban, triclosan
Breast creams (for use when nursing)
  Cetyl alcohol, cocoa butter, cod liver oil, dimethicone, glycerin, glyceryl monostearate, hard fat, lanolin, mineral oil, petrolatum, white petrolatum
Bunion remedies

Drawing salves (excluding products labeled for the treatment of boils in 21 CFR 310.531) —includes products labeled for the drawing or removal of splinters, slivers, or similar items
Ergot fluid extract, ichthammol, juniper tar (oil of cade), magnesium sulfate, pine tar, rosin, rosin cerate, sulfur
Foot balms, baths, and creams (excluding topical antifungal active ingredients in 21 CFR 310 545(a)(22) and 333 210) —including claims for relieving foot muscle strains and soreness from working out
Amyl salicylate, benzalkonium chloride, benzocaine, cajeput oil, carbolic acid, di-isobutyl phenoxy ethoxy ethyldimethyl benzyl ammonium chloride, essential oils, formalin, glyceryl monostearate, 8–hydroxyquinoline, iodized botanical oil, iron sulfate, isopropyl alcohol, lanolin, lithium chloride, magnesium sulfate, methyl salicylate, natural pine needle oil, o-benzyl-p-chlorophenol, oil of eucalyptus, oil of peppermint, oil of thyme, potassium iodide, propylene glycol, sodium bicarbonate, sodium chloride, sodium hypochloride, sodium lauryl sulfate, sodium sesquicarbonate, sodium sulfate, talc, tragacanth mucilage, trisodium phosphate, water soluble chlorophyllins, witch hazel, zinc oxide
Impotency cures
Yohimbine, yohimbine hydrochloride
Impregnated body wraps for weight reduction
Amino acids, collagen, magnesium sulfate
Lubricants and vaginal moisturizers
Benzoic acid, carbomer 934P, carbopol 940, chlorhexidine gluconate, glucono delta lactone, glycerin, hydrogenated palm oil glyceride, hydroxyethylcellulose, mineral oil, natrosol 250H, nonoxynol-9, polycarbophil, polysorbate 60, polyethylene glycol 300, polyquaternium, propylene glycol, sodium hydroxide, sorbic acid, sorbitol
Medicated bath preparations
Acetylated lanolin, alkyl aryl polyether alcohol, benzophenone-3, colloidal sulfur, cottonseed oil, di-isopropyl sebacate, dromotrizole, iron sulfate, isopropyl myristate, isopropyl palmitate, isostearic acid, lanolin alcohols extract, lanolin oil, liquid petrolatum, lithium chloride, magnesium sulfate, mineral oil, natural and essential oils, nonoxynol-5, octoxynol-3, PEG–4 dilaurate, PEG–8 dioleate, PEG–40 sorbitan peroleate, PEG–200 dilaurate, Peru balsam, PPG–15, pine needle oil, potassium iodide, stearyl ether oleth-2, sodium bicarbonate, sodium carbonate, sodium chloride, sodium hyposulfate, sodium lauryl sulfate, sodium sesquicarbonate, sodium sulfate, tar distillate, vitamin E, water soluble chlorophyllins
Nasal moisturizers
Glycerin, buffered isotonic saline solution, buffer solution, isotonic saline solution, normal saline, sodium chloride, saline phosphate
Nonantimicrobial skin wound cleansers (previously listed as "Detergents")
Tincture of Green Soap, phenol sodium, poloxamer 188
Prickly heat products
Aluminum hydroxide gel, zinc carbonate, zinc oxide
Skin protectant blister guard
Beta-hydroxyquinolone, eugenol, pyroxylin solution
Urethral creams for males
Urinary acidifiers
Ammonium chloride, ascorbic acid
Urinary alkalinizers
Sodium bicarbonate
Urinary analgesics/antiseptics

Benzoic acid, methenamine, methylene blue, phenazopyridine, phenazopyridine HCl, salicylamide, sodium salicylate
Wet dressings (excluding astringent active ingredients in 21 CFR 310.545(a)(18)(ii) and 347.10)
Aloe vera, calcium polysulfide, calcium thiosulfate, oxyquinoline sulfate, sodium propionate
Wound wash saline
Sodium chloride solution, sterile sodium chloride solution
Wrinkle removers
Alpha hydroxy acids
Alpha-hydroxycaprylic acid, alpha-hydroxyoctanoic acid, alpha-hydroxyethanoic acid and ammonium alpha-hydroxyethanoate, alpha hydoxy and botanical complex, glycolic acid, glycolic acid and ammonium glycolate, glycomer in crosslinked fatty acids alpha nutrium, hydroxycaprylic acid, L-alpha hydroxy acid, lactic acid, mixed fruit acid, sugar cane extract, tri-alpha hydroxy fruit acids, triple fruit acid
Beta hydroxy acids
Beta hydroxybutanoic acid, salicylic acid[1], trethocanic acid, tropic acid
Alpha and beta hydroxy acids
Citric acid, malic acid
Other ingredients
Egg albumin, magnesium aluminum silicate, protein, sodium silicate

[1] From a chemist's perspective, based on its chemical structure, salicylic acid is not a true beta hydroxy acid. However, cosmetic companies often refer to this ingredient as a beta hydroxy acid. Consequently, many consumers think of it as one as well.

III. Categories That Will Not Be Reviewed

A. Categories Reclassified or Considered as Foods

The categories "salt substitutes," "salt tablets," and "sweeteners" were included in the 1975 call-for-data notice (40 FR 38179 at 38183). These types of products are currently regulated as foods and will not be further considered as part of the OTC drug review. During the course of the review, several parties inquired whether "oral electrolyte replacement" products and "weight increasing" products would be included in the review because these product categories were not mentioned in the 1973 and 1975 call-for-data notices. Oral electrolyte replacement products intended to treat diarrhea are regulated as medical foods under section 529(b)(3) of the act (21 U.S.C. 360ee(b)(3) and 21 CFR 101.9(j)(8)), and products for "weight gain" are considered foods (21 U.S.C. 301 *et seq.*).

B. Categories Reclassified or Considered as Medical Devices

In several instances, since 1975, FDA determined that certain types of products previously regulated as drugs should be regulated as medical devices and changed its regulatory approach accordingly (Ref. 4). These products include a spray-on dressing that does not contain a drug component and a "device incorporating a drug component with the combination product having the primary intended purpose of fulfilling a device function." This latter group of products includes a skin closure or bandage with an antimicrobial agent and a wound dressing with an antimicrobial agent. These products are considered combination products regulated by the Center for Devices and Radiological Health (CDRH), using device authorities under the act.

A liquid bandage[5] is defined in 21 CFR 880.5090 as "a sterile device that is a liquid, semiliquid, or powder and liquid combination used to cover an opening in the skin or as a dressing for burns. The device is also used as a topical skin protectant." A medical adhesive tape and adhesive bandage is defined in 21 CFR 880.5240 as:

"* * * a device intended for medical purposes that consists of a strip of fabric material or plastic, coated on one side with an adhesive, and may include a pad of surgical dressing without a disinfectant. The device is used to cover and protect wounds, to hold together the skin edges of a wound, to support an injured part of the body, or to secure objects to the skin."

FDA is not including any of these device products in this current call for data.

[5]The categories "liquid bandages (sprays)—protective skin preparations" and "medicated bandages" were in the 1975 call-for-data notice (40 FR 38179 at 38181), which listed 23 active ingredients possibly used in these products. These ingredients in products for these specific uses would not be considered OTC drug active ingredients.

IV. Request for Data and Information

FDA invites the submission of data, published and unpublished, and other information, pertinent to all active ingredients in these and other eligible unreviewed OTC drug categories (see section II of this document). Interested persons should include any consumer comprehension data relating to the OTC use of drug products containing these ingredients. These data and information will contribute to the following objectives:

- Facilitate FDA's review and aid in its determination of whether these OTC drugs for human use are generally recognized as safe and effective and not misbranded under their recommended conditions of use, and

- Provide all interested persons an opportunity to present for consideration the best data and information available to support the stated claims for these products. Any relevant data and information on these drug products that may have been submitted to earlier rulemakings or in response to earlier call-for-data notices should be updated and resubmitted to facilitate FDA's review of these products.

FDA also requests manufacturers to identify other OTC drug products that still need to be reviewed to determine if they are GRAS/E for OTC use. For OTC drug products that should have been submitted for review but for which data and information have not been received, FDA may not consider those products to be GRAS/E for OTC use. In accordance with section 201(p) of the act, such drug products would be considered new drugs and would need an NDA to be marketed.

In the **Federal Register** of January 23, 2002 (67 FR 3060), FDA published a final rule providing additional criteria and procedures for classifying OTC drugs as GRAS/E and not misbranded. The procedures identified in that rule

apply to OTC drugs initially marketed in the United States after the OTC drug review began in 1972 and to OTC drugs without any U.S. marketing experience. This notice is not intended to apply to ingredients covered by the additional criteria and procedures identified in that rule.

This notice also does not apply to new chemical entities that have not previously been marketed for OTC use, regardless of the claims. These products should be submitted to FDA for evaluation in an NDA under 21 CFR part 314.

Manufacturers submitting data and information in response to this call for data should include any information (e.g., information showing when the product was first marketed in the United States) relating to the regulatory status of their product under the general regulatory policy described in the next section of this document. If such information does not exist or is found to be inadequate, such products may be at risk of regulatory action by FDA.

V. General Regulatory Policy

In order for a product to be eligible for the OTC drug review that began on May 11, 1972, the product or similarly formulated and labeled products had to be marketed as OTC drugs at the inception of the OTC drug review, which date was later extended to on or before December 4, 1975. Prescription drug products were also eligible for the review, as long as they continued to be marketed on a prescription basis while FDA evaluated data to ascertain whether the ingredient or combination of ingredients in the product could be proposed as GRAS/E for OTC use.

FDA may exercise its enforcement discretion to permit OTC drug products that do not have an approved NDA during the pendency of the OTC drug review to be marketed provided the following conditions are met:

1. The product or similarly formulated and labeled products were marketed as OTC drugs at the inception of the OTC drug review on May 11, 1972, a date that was later extended to on or before December 4, 1975 (see § 330.13).

2. Such product does not constitute a hazard to health.

3. The product formulation is not regarded regarded to be a prescription drug within the meaning of section 503(b) of the act (21 U.S.C. 353(b)).

4. The product is an OTC drug and does not bear claims for serious disease conditions that require the attention and supervision of a licensed practitioner.

To be considered in this review, eight copies of the data and information must be submitted, preferably bound, indexed, and on standard size paper (approximately 8½ by 11 inches). FDA suggests that all submissions be in the format described in § 330.10(a)(2).

In accordance with § 330.10(a)(2), FDA will handle all submitted data and information as confidential except the general comments submitted to the docket in response to this notice and the answers to the questions and specific information requested on phenazopyridine HCl in section II.B of this document. FDA wants the answers to the questions and the specific information on phenazopyridine HCl to be publicly available when it reviews this ingredient so that all interested parties will have access to this information and be able to participate fully in the deliberations. However, FDA will put all submitted data and information on public display in the Division of Dockets Management (see **ADDRESSES**) 30 days after publication of any proposed rules resulting from the review of the submitted material, except to the extent that the person submitting it demonstrates that it falls within the confidentiality provisions of 18 U.S.C. 1905, 5 U.S.C. 552(b), or section 301(j) of the act (21

U.S.C. 331(j)). At the time of publication, FDA will provide an address where requests for confidentiality should be submitted.

Data and information should be addressed to the Division of OTC Drug Products (see **ADDRESSES**). Data submitted after the closing of the comment period (see **DATES** section) will not be considered except by petition under 21 CFR 10.30. Interested persons may submit written or electronic comments to the Division of Dockets Management before the closing date. Three paper copies of all mailed comments are to be submitted. Individuals submitting written comments or anyone submitting electronic comments may submit one copy. Comments are to be identified with the docket number found in brackets in the heading of this document and may be accompanied by a supporting memorandum or brief. Received comments may be seen in the Division of Dockets Management between 9 a.m. and 4 p.m., Monday through Friday.

VI. References

The following references are on display in the Division of Dockets Management (see **ADDRESSES**) and may be seen by interested persons between 9 a.m. and 4 p.m., Monday through Friday.

1. "Bioassay of Phenazopyridine Hydrochloride for Possible Carcinogenicity," National Cancer Institute Carcinogenesis Technical Report Series No. 99, U.S. Department of Health, Education, and Welfare, Publication No. NIH 78–1349, 1978.

2. Labeling for Uristat (Urinary Pain Relief Tablets).

3. Food and Drug Administration, Compliance Policy Guides, No. 7132b.04, issued October 1, 1980, revised May 22, 1987.

4. Food and Drug Administration, Intercenter Agreement Between the Center for Drug Evaluation and Research and the Center for Devices and Radiological Health, October 31, 1991.

Dated: 12/22/03

December 22, 2003.

Jeffrey Shuren,
Assistant Commissioner for Policy.

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