



June 24, 2004

Division of OTC Drug Products (HFD-560)
Center for Drug Evaluation and Research
Food and Drug Administration
5600 Fishers Lane
Rockville, MD 20857

Re: Response to Request for Data and Information published in Federal Register Vol. 68, No. 250 pp.75585-75591 for section F. Lubricants and Vaginal Moisturizers

Dear Sir or Madam:

In the above reference request for data FDA declares that “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).” This statement ignores several facts and makes a couple of unsupported assumptions. It is our conviction that these claims are not inherently “drug claims”, could be “device claims” depending on the product, but are more consistent with claims for cosmetic products.

The belief or assumption that relief of discomfort or facilitating the ease of sexual activity is exclusively related to disease ignores the natural biological (hormonal) changes that occur as women progress from puberty through menopause. FDA has recognized these changes when it has approved hormone replacement products for postmenopausal women during the last 20 years (Physician's Desk Reference 1983 - 2003). These hormonal changes can result in vaginal dryness for some women because of a decrease in the elasticity of the vaginal tissues, and the reduced amount of cervical mucus that is produced. Vaginal lubrication during intercourse is also affected by these hormonal changes. These hormonal changes also occur in women who have had bilateral oophrectomy or are receiving medical treatment which has an antiestrogenic effect. Additionally, not all women of the same age produce similar amounts of vaginal lubrication when sexually aroused. This may be due to nutritional, general health or daily stress, which are not defined as diseases. Finally, not all couples in every act of coitus desire to wait for full vaginal lubrication before attempting intercourse. In these instances of low vaginal lubrication friction makes penetration difficult and may be uncomfortable. Most instances of low or no vaginal lubrication are not related to any disease, but due to normal hormonal changes or variations among women, or the desire to have intercourse prior to vaginal lubrication due to foreplay. The products that make the above-sited claims address these circumstances.

These products work by reducing friction similar in principle to the function of motor oil in cars or machining fluids in metalworking. They do not achieve their intended function as drug products do through chemical action within or on the body and are not required to be metabolized to achieve their intended purpose. They do not affect the intrinsic structure or function of any part of the body. These products are like skin creams used for dry skin that claim they provide smooth silky skin. They are topically applied like cosmetics and are not absorbed



RECEIVED
JUL 22 2004
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16 July 2004

To Whom it may concern:

Instead, Inc. attempted to meet the June 28, 2004 deadline for OTC Drug FDA request for data and information published in Federal Register Vol. 68, No. 250 pp. 75585-75591 for section F. Lubrications and Vaginal Moisturizers. To ensure prompt delivery we had originally shipped via Fed-Ex to the address noted on the FDA instructions on 24 June 2004. We received the package "Return to Sender; undeliverable address" on 8 July 2004. We called the Division of OTC and were notified that the original address could not accept overnight mail, only USPS. We are resubmitting this information for review.

Sincerely,

Instead, Inc.



Original Shipment Envelope
Sent 25 June 2004

FedEx Urgent

136596 9/00 MWI

Name
Company

Address

City, State, Zip

Telephone

(301) ~~827-2222~~

Page 1 of 1

FedEx | Ship Manager | Label 7912 7979 1978

From: Origin ID: (858)550-1901
Natalie Spencer
INSTEAD, INC
4275 EXECUTIVE SQUARE
SUITE 1000
LA JOLLA, CA 92037

FedEx
Express



CLASS 0000

SHIP TO: (858)550-1901

BILL SENDER

Drug Evaluation and Research Food a
Division of OTC Drug Products
5600 Fishers Lane

Rockville, MD 20857

Ship Date: 24JUN04
Actual Wgt: 1 LB
System#: 3690755/INET1850
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Delivery Address Bar Code

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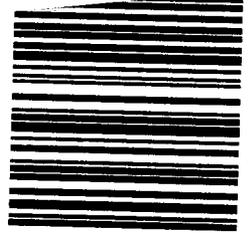
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Track Shipments
Detailed Results



Tracking number	791279791978	Delivery location	ROCKVILLE MD
Ship date	Jun 24, 2004	Service type	Priority Envelope

Date/Time	Status	Location	Comments
Jul 6, 2004 10:42 am	Package status	ROCKVILLE MD	Pkg returned to shipper
Jul 3, 2004 9:22 am	Package status	ROCKVILLE MD	Package in FedEx location
Jul 2, 2004 6:31 pm	Package status	ROCKVILLE MD	Package in FedEx location
Jul 1, 2004 5:41 pm	Package status	ROCKVILLE MD	Package in FedEx location
Jun 30, 2004 6:54 pm	Package status	ROCKVILLE MD	Package in FedEx location
Jun 29, 2004 6:23 pm	Package status	ROCKVILLE MD	Package in FedEx location
Jun 28, 2004 5:05 pm	Package status	ROCKVILLE MD	Package in FedEx location
Jun 26, 2004	8:34 am	ROCKVILLE MD	Delivery attempt
	9:48 am	ROCKVILLE MD	Package in FedEx location
	8:49 am	ROCKVILLE MD	Package not due for delivery
	7:49 am	DULLES VA	Left FedEx Ramp
	7:48 am	ROCKVILLE MD	Arrived at FedEx Destination Location
7:18 am	DULLES VA	Arrived at FedEx Ramp	

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Add a message to this email.

From

To

Send email

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Align top of FedEx Shipping Label or ASTRA Label here.

Returned Fed-ex
Envelope
8 July 2004

Ref: RTS 791279791978
Dept: RTS

Date: 06JUL04 SHIPPING \$0.00
Wgt: 1 LBS SPECIAL \$0.00
HANDLING \$0.00
TOTAL \$0.00

SERVICE: ** 2DAY **
TRACK: 6571 7983 9861

ORIGIN ID: EDGA (800) 463-3339
CUSTOMER SERVICE
FDX/GAIA STATION
7331 CALHOUN PLACE
ROCKVILLE, MD 20855

SHIP DATE: 06JUL04
SYSTEM #311457 / CAFE2208
ACTUAL WGT: 1 LBS MAN-WGT
ACCOUNT #: 114219789

FedEx



FedEx Revenue Barcode

TO:

RETURN
NATALIE SPENCER
INSTEAD INC
4275 EXECUTIVE SQ STE 1000
LA JOLLA, CA 92037

BILL RECIPIENT

REF: RTS 791279791978



Delivery Address Barcode (FedEx-EDR)

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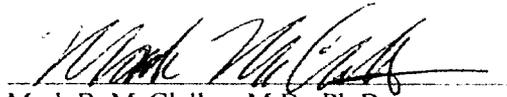
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This MOU does not modify existing cooperative activities nor does it preclude entering into separate arrangements for special programs that can be handled more efficiently and expeditiously by special arrangements.

Nothing in this MOU is intended to diminish or otherwise affect the authority of either Participant to carry out its regulatory responsibilities and programs. In addition, no provision of this MOU restricts either Participant from conducting its own inspection of a therapeutic product manufacturing facility within the jurisdictional boundaries of the other country when needed to meet the needs of its own regulatory programs.

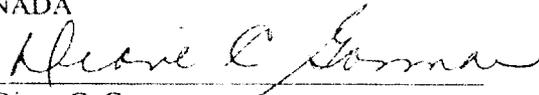
Signed at Ottawa, Canada on this eighteenth day of November 2003 in duplicate in the English language.

FOR THE FOOD AND DRUG ADMINISTRATION
DEPARTMENT OF HEALTH AND HUMAN SERVICES
OF THE UNITED STATES OF AMERICA



Mark B. McClellan, M.D., Ph.D.
Commissioner of Food and Drugs

FOR THE HEALTH PRODUCTS AND FOOD BRANCH
HEALTH CANADA
OF CANADA



Diane C. Gorman,
Assistant Deputy Minister

[FR Doc. 03-32104 Filed 12-30-03; 8:45 am]
BILLING CODE 4160-01-C

**DEPARTMENT OF HEALTH AND
HUMAN SERVICES**

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

A. Nasal Moisturizer Drug Products

The agency considers nasal moisturizer products⁴ 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"
- "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.

⁴In 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.

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 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

⁴A product containing methanamine, 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.

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 CARCINOGENESIS 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

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 alkylaryl polyether 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, drometizole, 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 alkalizers

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

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 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: December 22, 2003.

Jeffrey Shuren,

Assistant Commissioner for Policy.

[FR Doc. 03-32102 Filed 12-30-03; 8:45 am]

BILLING CODE 4160-01-8

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration

[FDA 225-04-8002]

Exchange of Letters Between the Food and Drug Administration and the European Commission and the European Agency for the Evaluation of Medicinal Products Concerning the Sharing of Documents and/or Information Related to Assuring the Safety, Quality, and Efficacy of Pharmaceutical Products Intended for Human or Animal Use

AGENCY: Food and Drug Administration, HHS.

ACTION: Notice.

SUMMARY: The Food and Drug Administration (FDA) is providing notice of an exchange of letters between FDA and the European Commission and the European Agency for the Evaluation of Medicinal Products (EMA). The participants concluded this exchange of letters on September 12, 2003. These letters express the intentions of FDA, the European Commission, and EMA to continue cooperative activities to further enhance and strengthen communication between the respective organizations and further enhance public health promotion and protection in the European Union and the United States of America.

DATES: The agreement became effective September 12, 2003.

FOR FURTHER INFORMATION CONTACT: Michelle Limoli, European Commission Office of International Programs (HFC-1), Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857, 301-827-0908.

SUPPLEMENTARY INFORMATION: In accordance with 21 CFR 20.108(c), which states that all written agreements and memoranda of understanding between FDA and others shall be published in the *Federal Register*, the agency is publishing notice of this exchange of letters.

Dated: December 18, 2003

Jeffrey Shuren,

Assistant Commissioner for Policy.

BILLING CODE 4160-01-5