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June 28, 2004

BY HAND DELIVERY

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

Re: Docket No. 2003N-0539: Over-the-Counter Drug Products; Safety and Efficacy Review

Dear Sir or Madam:

On behalf of CooperSurgical, and in response to the Food and Drug Administration's ("FDA's" or "the Agency's") December 31, 2003 call for data on over-the-counter ("OTC") drug products, we are writing to request that the ingredients sodium lauryl sulfate and hydroxyquinoline sulfate,^{1/} individually and in combination, be included in the OTC drug monograph for vaginal lubricants and moisturizers. These ingredients are eligible for the OTC drug review and are not currently contemplated in other FDA OTC monographs.

CooperSurgical manufactures and markets pharmaceuticals, medical devices, diagnostic products, surgical instruments and accessories for the women's healthcare market. CooperSurgical has headquarters and manufacturing facilities in Trumbull, Connecticut; it also conducts manufacturing activities in Bedminster, New Jersey; Cranford, New Jersey; Fort Atkinson, Wisconsin; Malmo, Sweden; Montreal, Canada and Berlin, Germany. In February

^{1/} Hydroxyquinoline sulfate is also known as: oxyquinoline sulfate, 8-hydroxyquinoline sulfate, hydroxy-8-quinolinium sulfate, and oxine sulfate.

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2004, CooperSurgical acquired the assets of Milex Products, Inc. ("Milex"), including a lubricating vaginal jelly product, Trimo-San, which contains sodium lauryl sulfate and hydroxyquinoline sulfate as active ingredients. CooperSurgical is submitting these comments for the purpose of seeking to include the active ingredients sodium lauryl sulfate and hydroxyquinoline sulfate, and combinations of both ingredients, as generally recognized as safe and effective in FDA's OTC monograph for lubricants and vaginal moisturizers. Additionally, CooperSurgical seeks to include the claims identified below in FDA's OTC monograph for lubricants and vaginal moisturizers.

II. Description of Product/Ingredients

Trimo-San is a vaginal jelly composed of the active ingredients sodium lauryl sulfate (0.01%) and hydroxyquinoline sulfate (0.025%). Trimo-San is currently marketed with the following claims: (1) to help restore and maintain normal vaginal acidity; and (2) to coat the walls of the vagina with a lubricating film that helps reduce odor-causing bacteria. Trimo-San was originally marketed by Milex prior to 1969; was reformulated to add hydroxyquinoline sulfate as an active ingredient in 1977, and has been marketed without interruption since.^{2/} The product is labeled for use with a vaginal pessary.^{3/} It is recommended in the product labeling that in the first week after insertion of the pessary, Trimo-San should be used three times (or as otherwise directed by a healthcare professional); after the first week of treatment, two applications per week are recommended (or as otherwise directed by a healthcare professional). Copies of the product labeling are included at Attachment 1. As discussed more fully below, the product has a long marketing history. CooperSurgical has no knowledge of any reports of adverse events involving Trimo-San, nor is the Company aware of any reports of overdose or toxicity resulting from its use.

III. Scientific Support of Safety and Effectiveness of Proposed Active Ingredients Individually and in Combination for Vaginal Use

Considerable scientific support exists for the inclusion of sodium lauryl sulfate and hydroxyquinoline sulfate as active ingredients individually and in combination in OTC drug

^{2/} Note that this reformulation was to replace phenylmercuric acetate; it is CooperSurgical's understanding that FDA removed this active ingredient from the market at that time. The product was also reformulated in 1963, 1969 (twice), 1980, 1984 (twice), 1988 and 1997, to add or modify inactive ingredients. While the inactive ingredients are not directly relevant to FDA's OTC process, which primarily reviews active ingredients for OTC drug products, we are providing this information for the purpose of providing a complete record.

^{3/} A vaginal pessary is a removable structure placed in the vagina to support the pelvic organs and is used to treat conditions such as uterine prolapse (falling down of the uterus), uterine retroposition (backward displacement), or gynecologic hernia. 21 C.F.R. § 884.3575.

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products for vaginal use, specifically in lubricants and moisturizers. We have summarized below the scientific support for the general recognition of safety and effectiveness of sodium lauryl sulfate and oxyquinoline sulfate, and for the two ingredients in combination, for this vaginal use.

A. Sodium Lauryl Sulfate

In an advance notice of proposed rulemaking ("ANPRM") for vaginal drug products, published in 1983, sodium lauryl sulfate was categorized as Category I for safety and effectiveness in vaginal douches at a concentration of 0.01 to 0.02 % to produce a mucolytic effect.^{4/} This demonstrates the safety of the ingredient in similar concentrations for other types of OTC drug products used in the vaginal area. The amount of sodium lauryl sulfate in Trimo-San (0.01%) is within the FDA Advisory Panel's identified acceptable limits. In addition, the 2001 Cosmetic Ingredient Review ("CIR") Compendium lists sodium lauryl sulfate as safe in formulations of less than 1% for products intended for prolonged contact with skin.

B. Hydroxyquinoline Sulfate

Oxyquinoline compounds are widely known for their antimicrobial and antifungal properties, and have been used for decades in various topical preparations.^{5/} In 1983, FDA's Advisory Panel concluded that the data were insufficient to establish the safety and effectiveness of oxyquinoline compounds for the relief of minor irritations of the vagina.^{6/} The FDA Advisory Panel recommended that oxyquinoline sulfate be used in douches at a concentration of 2%, and that such products be labeled for the relief of minor irritations of the vagina; however, the ingredient was classified as Category III because the data were inconclusive.^{7/} The FDA

^{4/} Category I conditions are those under which FDA's Advisory Review Panel on Contraceptives and Other Vaginal Drug Products ("the Advisory Panel" or "the Panel") found vaginal drug products to be generally recognized as safe and effective and not misbranded. Vaginal Drug Products for Over-the-Counter Human Use; Establishment of a Monograph, 48 Fed. Reg. 46694, 46706 (Oct. 13, 1983). As will be discussed more fully below, this monograph was withdrawn by the Agency in 1994, and the claims and ingredients were dispersed to four other OTC monographs. However, vaginal use of the ingredients oxyquinoline sulfate and sodium lauryl sulfate have not been considered as part of these other monographs.

^{5/} See, e.g., Minnich, S.M., et al. 1991. Effect of oxyquinoline ointment on diaper dermatitis. Dermatol. Nurs. 3(1):25-8, 40 (Attachment 2).

^{6/} The FDA Advisory Panel expressed concern that the carcinogenic potential of oxyquinoline compounds was unresolved, because some studies the Panel reviewed indicated carcinogenic potential while others did not. Thus, the Panel recommended that oxyquinoline compounds be subjected to carcinogenicity testing. 48. Fed. Reg. 46694, 46715-16 (Oct. 13, 1983).

^{7/} 48 Fed. Reg. 46694, 46716 (Oct. 13, 1983).

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Advisory Panel also noted that oxyquinoline compounds were extensively used in the 1930's and 1940's for the treatment of gonorrhea and other infections. To evaluate this use, oxyquinoline compounds were applied to the urethra and vagina in repeated, concentrated doses, with no reported adverse reactions.^{8/} This data supports the safety of the vaginal application of oxyquinoline sulfate.

The published literature further supports the safety of oxyquinoline when topically applied to skin for a variety of skin conditions and lesions.

Minnich et al.^{9/} studied the safety and effectiveness of a single application of an ointment containing 0.22% oxyquinoline for the treatment of diaper dermatitis in a randomized double-blind trial of 17 infants. Infants treated with either Desitin[®] or A&D[®] ointments served as controls. The results of this study demonstrated that diaper dermatitis in infants treated with the oxyquinoline-containing ointment was significantly improved as compared to the control groups, and there were no side effects or worsening of the rash in any of the infants treated with the oxyquinoline-containing ointment. These data further support the safety of oxyquinoline sulfate in the vaginal area.

In another study, significantly more healing, as well as more rapid healing, of Stage I and Stage II skin lesions was observed in nursing home residents treated with DermaMend[™] (an oxyquinoline-containing ointment, n=55) than with residents treated with A&D[®] ointment (n=27) for 28 days in a randomized double-blind trial.^{10/} A combination of 0.5% potassium hydroxyquinoline sulfate and 1% hydrocortisone in a cream base, when applied to either patients with infected eczema (n=76) or impetigo (n=43) for two weeks resulted in marked clinical and bacteriological improvement or cure in 90% and 92% of patients treated, respectively, with no reports of systemic or local side effects.^{11/} These same investigators reported significant clinical

8/ 48 Fed. Reg. 46694, 46716 (Oct. 13, 1983) (citing Diasio, J.S. 1932. A new bactericide for treating anterior gonorrhea. Military Surgeon. 70:594-596; Diasio, J.S. 1933. Present status of treatment of endocervicitis. Military Surgeon. 137:246-248; and Davin, E.J. and Schlauch, T.S. 1932. The use of oxyquinoline tartrate in gynecology – a new antiseptic: preliminary survey of eighty-five cases. Am. Medicine. 38:9-22).

9/ Minnich, S.M., et al. 1991. Effect of oxyquinoline ointment on diaper dermatitis. Dermatol Nurs. 3(1):25-8, 40.

10/ Gerding, G.A., and Browning, J.S. 1992. Oxyquinoline-containing ointment vs. standard therapy for Stage I and Stage II skin lesions. Dermatol. Nursing. 4(5):389-98 (Attachment 3).

11/ Jaffé, G.V., and Grimshaw, J.J. 1986. A clinical trial of hydrocortisone/potassium hydroxyquinoline sulfate ('Quinocort') in the treatment of infected eczema and impetigo in general practice. Pharmatherapeutica. 4(10):628-36 (Attachment 4).

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improvement in acne vulgaris lesions in a double-blind trial of 52 patients treated with a combination of 0.5% potassium hydroxyquinoline sulfate and 10% benzoyl peroxide with or without 1% hydrocortisone as compared to vehicle or 10% benzoyl peroxide alone twice daily for 12 weeks, with no reports of adverse effects.^{12/} Taken together, the results of these studies provide supportive evidence of the safety and effectiveness of oxyquinoline preparations when topically applied to breached skin.

In 1992, the Cosmetic Ingredient Review Expert Panel (“CIR”) reviewed the safety of oxyquinoline and oxyquinoline sulfate for use as a fungicide and bactericide in cosmetic formulations at concentrations $\leq 1.0\%$.^{13/} The CIR concluded that available carcinogenicity and sensitization test data “are insufficient to support a conclusion on the safety of oxyquinoline and oxyquinoline sulfate as used in cosmetic products,” and that skin carcinogenicity studies in one animal species, as well as human irritation and sensitization studies were needed before safety conclusions can be made.^{14/} Despite this conclusion, the CIR noted that oxyquinoline compounds are non-toxic in acute or subchronic toxicity studies, and that oral carcinogenicity studies in rodents are negative.

Given the CIR’s recognition that the data were inconclusive, the negative results in all reported animal toxicity studies, and the long history of safe clinical use described above, CooperSurgical believes that oxyquinoline compounds are safe when topically applied. Moreover, these supportive safety data from skin application (particularly breached skin) reasonably can be extrapolated to vaginal products containing oxyquinoline sulfate. Like the epidermis of skin, the vaginal mucosa in sexually mature women is comprised of stratified squamous epithelium.^{15/} While skin epidermis is keratinized, and therefore more impermeable, and vaginal mucosa is not keratinized, breached skin (*i.e.*, rashes and skin lesions) where the epidermal layer is compromised, more closely approximates the permeable non-keratinized epithelium of the vaginal mucosa. Thus, the published literature provides supportive evidence that oxyquinoline sulfate, when topically applied to vaginal mucosa, does not elicit adverse local or systemic effects.

^{12/} Jaffé, G.V., et al. 1989. Benzoyl peroxide in the treatment of acne vulgaris: a double-blind, multi-centre comparative study of ‘Quinoderm’ cream and ‘Quinoderm’ cream with hydrocortisone versus their base vehicle alone and a benzoyl peroxide only gel preparation. *Curr. Med. Res. and Opinion.* 11(7):153-62 (Attachment 5).

^{13/} Cosmetic Ingredient Review Expert Panel. 1992. Final report on the safety and assessment of oxyquinoline and oxyquinoline sulfate. *J. Amer. Coll. Toxicol.* 11(4):497-507 (Attachment 6).

^{14/} *Id.*

^{15/} See generally Vaginal Contraceptive Drug Products for Over-the-Counter Human Use; Establishment of a Monograph; Proposed Rulemaking, 45 Fed. Reg. 82014, 82018-20 (Dec. 12, 1980).

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Moreover, CooperSurgical is aware of other currently marketed vaginal lubricants formulated with oxyquinoline sulfate 0.025% as an active ingredient. Ortho Pharmaceutical Corporation (“Ortho”) markets ACI-JEL vaginal jelly to restore and maintain normal vaginal acidity through its buffer action.^{16/} In its patient information, Ortho states that no serious adverse reactions or potential safety hazards have been reported with the use of ACI-JEL, which is recommended for twice-daily administration, which is more frequent than that recommended for Trimo-San. The existence of vaginal products that contain oxyquinoline sulfate as an active ingredient at the same concentration as that used in Trimo-San, and that are marketed with similar claims, lends additional support to the conclusion that the ingredient is safe and effective for vaginal use. Thus, oxyquinoline sulfate should be included as an active ingredient in FDA’s OTC drug product monograph for lubricants and vaginal moisturizers.

C. Sodium Lauryl Sulfate and Hydroxyquinoline Sulfate are Safe and Effective in Combination for OTC Lubricants and Vaginal Moisturizers

The combination of the active ingredients sodium lauryl sulfate and hydroxyquinoline sulfate is also safe and effective for use in OTC lubricants and vaginal moisturizers. The combination of these ingredients has a long history of marketing and use,^{17/} and CooperSurgical has no knowledge of any adverse events associated with the product and has received no reports of overdose or toxicity from its use.^{18/} In fact, during a recent meeting between officials of FDA’s Chicago District Office and CooperSurgical, representatives of FDA’s Chicago District indicated that they had no safety concerns regarding Trimo-San. Further, a number of published literature references recommend the use of these combined active ingredients in Trimo-San for use with vaginal pessaries for the purpose of lubrication, the reduction of bacteria, odor and discharge,

^{16/} See Attachment 7.

^{17/} As previously stated, Trimo-San has been marketed with this combination of active ingredients since 1977.

^{18/} These statements are based on CooperSurgical’s knowledge, based upon a review of Milex’s files and information obtained from Milex representatives.

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and the relief of minor irritation and itching.^{19/} In addition, testimonials from physicians provide further evidence of the safe and effective use of these active ingredients in combination, in Trimo-San, for lubrication, to maintain normal vaginal pH, and to assist with non-specific and monilial vaginitis.^{20/} Therefore, FDA should include the combination of sodium lauryl sulfate and hydroxyquinoline sulfate in the OTC drug product monograph for lubricants and vaginal moisturizers.

IV. The Inclusion of Sodium Lauryl Sulfate and Hydroxyquinoline Sulfate Individually and in Combination in an FDA Monograph on Lubricants and Vaginal Moisturizers is Proper

CooperSurgical believes that sodium lauryl sulfate and hydroxyquinoline sulfate individually and in combination properly should be included in an FDA OTC drug monograph on lubricants and vaginal moisturizers. Regulatory and policy reasons support the inclusion of these two active ingredients for this type of use.

Both ingredients were originally considered in FDA's 1983 ANPRM for vaginal drug products, demonstrating that the Agency believes that they are appropriately part of the OTC review process. The 1983 ANPRM was withdrawn in 1994, and products were divided into other OTC monographs.^{21/} FDA stated that, "specific claims and ingredients [evaluated in the 1983

^{19/} Jenkins, P. et al. 2003. Pessaries. *Procedures for Primary Care*. 1171-1180; Farrell, S.A. 2003. Nonsurgical management of pelvic organ prolapse. *Ostergard's Urogynecology and Pelvic Floor Dysfunction*, 5th edition. 393-407; Bent, A.E. and McLennan, M.T. 1996. Geriatric urogynecology. *Urogynecology and Urodynamics Theory and Practice*, 4th edition. 447-479; Bash, K.L., M.D. 2000. Review of vaginal pessaries. *Obstetrical & Gynecological Survey*. 55(7):455-460; Viera, A.J. and Larkins-Pettigrew, M. 2000. Practical use of the pessary. *Am. Family Physician*. 61(9):2719-2726; Deger, R.B., et al. 1993. The vaginal pessary: past and present. *Postgraduate Obstetrics & Gynecology*. 13(18):1-7; Farrell, S.A. 2001. Pessaries for the management of stress urinary incontinence. *J. Obstetrics & Gynecology of Canada*. 23(12):1184-1189 (Attachment 8).

^{20/} Letter from Ralph W. Hale, M.D., Chairman and Professor, University of Hawaii at Manoa, John A. Burns School of Medicine, Department of Obstetrics and Gynecology, to Bipin Desai, Milex Western (May 28, 1992); Letter from James C. Caillouette, M.D., F.A.C.O.G., F.A.C.S., to FDA (June 17, 2004); and Memorandum from William E. Caughman, Chief Pharmacist, Office of District Management, South Carolina Department of Health and Environmental Control, to South Carolina Department of Health and Environmental Control Officials (Apr. 12, 1978) (Attachment 9).

^{21/} Vaginal Drug Products for Over-the-Counter Human Use; Withdrawal of Advance Notice of Proposed Rulemaking, 59 *Fed. Reg.* 5226 (Feb. 3, 1994). The four other monographs were: antifungal drug products, external analgesic drug products, skin protectant drug products, and topical antimicrobial drug products.

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ANPRM] for use in and around the vagina will be included in other appropriate OTC drug rulemakings.^{22/} Sodium lauryl sulfate and hydroxyquinoline sulfate have not yet been addressed in these other OTC monographs to date. Accordingly, given the uses of these active ingredients, CooperSurgical believes they should be included in this monograph for lubricants and vaginal moisturizers. FDA withdrew the vaginal drug products monograph with the intention that the drug products and ingredients would be included in future OTC rulemakings.

Additionally, in the Agency's last official position with respect to these active ingredients, sodium lauryl sulfate was Category I and oxyquinoline sulfate was Category III, indicating that vaginal uses of these active ingredients were recognized by others as safe and effective or that more data was warranted at the time. Therefore, both ingredients have been under consideration for vaginal use, and this review will enable that process to continue.^{23/} FDA's December 31, 2003 call for data seeks to obtain information regarding the product categories of lubricants and vaginal moisturizers which were not addressed in the 1983 ANPRM. As vaginal lubricating ingredients that properly should be part of the OTC review, these products should be considered as part of this monograph.^{24/}

V. Summary/Conclusion

For the foregoing reasons, it is appropriate to include sodium lauryl sulfate and hydroxyquinoline sulfate, individually and in combination, in the OTC drug monograph for lubricants and vaginal moisturizers. Additionally, claims regarding restoring and maintaining normal vaginal acidity and the use of these ingredients in combination to create a lubricating film that reduces odor-causing bacteria should also be included in this monograph. Products containing these ingredients are safe and effective for vaginal use, and have a long history of safe and effective use to support such marketing.

^{22/} 59 Fed. Reg. 5226, 5234 (Feb. 3, 1994).

^{23/} Oxyquinoline sulfate was found to be Category III for the relief of minor irritations of the vagina; however, this is not the indication for Trimo-San. Thus, use of oxyquinoline sulfate for Trimo-San's intended use has not been evaluated by FDA.

^{24/} "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." 68 Fed. Reg. 75585, 75588 (Dec. 31, 2003).

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Should you have any questions regarding these comments, please do not hesitate to contact me.

Sincerely,



Sandra J.P. Dennis
Counsel for CooperSurgical

Attachments

c: Nicholas Pichotta
President
CooperSurgical

John Chapman, RAC
Manager, Regulatory Affairs
CooperSurgical