

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: April 8, 2004

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SUBJECT: HISTORY AND OVERVIEW OF OTC MONOGRAPH FOR
TOPICAL ANTIFUNGAL DRUG PRODUCTS

Introduction

Over-the-counter (OTC) drug products can be marketed under two regulatory mechanisms:

- (1) a new drug application (NDA)
- (2) OTC drug monograph system

This discussion will focus on the OTC drug monograph system. More specifically, the OTC drug monograph for topical antifungal products will be discussed, with emphasis on those products used to treat athlete's foot (tinea pedis).

OTC Drug Monograph System

The OTC drug review began in 1972 as a review of the safety and effectiveness of OTC drugs on the market at the time. This marked the beginning of the OTC drug monograph system. FDA (we) initiated the OTC drug review by identifying a number of therapeutic categories for which we would establish OTC drug monographs. The OTC drug monograph system gives manufacturers a mechanism to market OTC drug products without needing a new drug application (NDA). Unlike OTC drug products marketed under an NDA, products marketed under an OTC drug monograph do not need pre-approval from FDA. OTC drug monographs list the conditions of use under which a drug product is generally recognized as safe and effective (GRASE). The conditions of use include active ingredients (single or in combination), dosage strength, dosage form (in some cases), indications, warnings, directions for use, and, in some cases, final formulation testing.

The OTC drug review is a four step public rulemaking process:

- (1) Advisory Review Panel: The Panel is a group of experts in a particular OTC drug category. The Panel reviews data for OTC drug products marketed prior to December 1975 and recommends GRASE conditions for an OTC drug monograph.

- (2) Advance Notice of Proposed Rulemaking (ANPR): FDA publishes the ANPR in the *Federal Register* to announce its intention of creating an OTC drug monograph. The ANPR also contains the Panel's report, which lists the recommended GRASE conditions. Following publication of the ANPR, interested persons may submit comments and additional data regarding the Panel's recommendations during a 90-day comment period.
- (3) Tentative Final Monograph (TFM): FDA publishes the TFM, or proposed rule, in the *Federal Register* as its preliminary position regarding the safety and effectiveness of each active ingredient in a therapeutic category. The TFM is based on FDA's interpretation of data provided to the Panel, the Panel's recommendations, and any new data submitted in response to the ANPR. Following publication of the TFM, there is a 90-day comment period.
- (4) Final Monograph (FM): FDA reviews all comments and data submitted during the TFM comment period and amends the TFM to create the FM, or final rule, which is published in the *Federal Register*. The monograph is a set of regulations included in the Code of Federal Regulations. The FM includes an effective date, after which drug products marketed under the monograph must comply with the conditions of use described in the monograph.

Each step in the process builds upon and is a continuation of the previous step. Although the FM is the final step in this OTC drug review process, FDA can amend the FM to include additional GRASE conditions (e.g., add a new active ingredient).

History of OTC Topical Antifungal Monograph

Advanced Notice of Proposed Rulemaking

The ANPR was published on March 23, 1982 (Ref. 1). The Panel reviewed approximately 50 clinical studies along with *in vitro* and animal studies to assess the safety and effectiveness of about 35 topical antifungal ingredients. Of these clinical studies, roughly ten were designed to demonstrate the effectiveness of active ingredient(s) in treating athlete's foot.

The Panel expressed concerns about the ingredients only mitigating the symptoms rather than curing the condition, as apparent by the statement that, in order to best serve all consumers, "an OTC product must provide more than temporary symptomatic relief of athlete's foot, jock itch, and ringworm" (Ref. 1, page 12489). The Panel required at least one well-designed clinical study demonstrating that an active ingredient treats athlete's foot as evidence of effectiveness. In reviewing the clinical trials, the Panel defined a well-controlled study as one that met the following six criteria (Ref. 1, pages 12491-92):

- (1) double-blinded and randomized
- (2) vehicle-controlled
- (3) test groups of adequate size

- (4) entry criteria based on clinical sign and symptoms with diagnosis verified by positive potassium hydroxide (KOH) preparation and positive culture (confirming the presence of fungus)
- (5) standardized dosing regimen (*i.e.*, at least four week treatment for athlete's foot)
- (6) follow-up examinations performed at the end of treatment and final evaluation of clinical results corroborated by negative KOH and negative culture two weeks after therapy ends

The Panel recommended an ingredient as GRASE for the treatment of athlete's foot if it was significantly more effective than vehicle. The Panel also reviewed clinical studies meeting this criterion that demonstrated tolnaftate is effective in the prevention of athlete's foot and recommended the prevention claim for this ingredient.

A relatively small percentage of the studies submitted to FDA actually met these criteria. There was considerable variability in the study protocols. Enrollment for most of the clinical studies submitted to the Panel was based on diagnosis of tinea pedis by a physician. In a third of the studies that included physician diagnosis, the diagnosis was confirmed by positive KOH and culture. Treatment duration varied between 2 to 6 weeks with the treatment duration being 4 weeks in the majority of studies. These studies also assessed efficacy at different time points and used different criteria for cure. All of these factors make it difficult to compare the cure rates of the monograph products to those of the NDA products because of differences in the design of the clinical studies.

In addition, the Panel proposed the idea of simple and concise labeling that "should enable the consumers to clearly understand the results that can be anticipated from the use of the product" (Ref. 1, page 12490). Examples of indications recommended by the Panel included the following (Ref. 1, page 12565):

- "treats athlete's foot"
- "for the treatment of athlete's foot and for the relief of itching"

Labeling for products used for the treatment of athlete's foot should include the following warning (Ref. 1, page 12565):

"If irritation occurs or if there is no improvement within 4 weeks, discontinue use and consult a doctor or pharmacist".

Furthermore, the Panel stated that "the directions for use should be clear and direct. They should provide the user with sufficient information to enable safe and effective use of the product" (Ref. 1, page 12490).

Based on the clinical studies, which generally involved four weeks of treatment, the Panel determined that OTC topical antifungal drug products are most effective in treating athlete's foot with application twice per day for 4 weeks. The Panel recommended that six active ingredients be classified as GRASE based on their review of the studies.

Tentative Final Monograph

The TFM, or proposed rule, was published on December 12, 1989 (Ref. 2). In the TFM, we discussed 25 clinical studies submitted following publication of the ANPR. Six of the 25 studies addressed athlete's foot. Based on these studies, we agreed with the Panel's recommended conditions of use except with regard to two active ingredients. We disagreed with the Panel and did not propose nystatin as GRASE. We also proposed to include povidone-iodine as GRASE based on clinical studies.

Final Monograph

The FM, or final rule, was published on September 23, 1993, and became effective on September 23, 1994 (Ref. 3). In the FM, we reviewed about ten studies and found the following active ingredients to be GRASE for the treatment of athlete's foot:

- clioquinol 3%
- haloprogin 1%
- miconazole nitrate 2%
- povidone-iodine 10%
- tolnaftate 1%
- undecylenic acid and its salts (calcium, copper, and zinc) for a total undecylenate concentration of 10-25%

We found all other ingredients considered in this rulemaking not to be GRASE for use in an OTC topical antifungal drug product. In addition, the FM includes labeling similar to that recommended by the Panel in the ANPR. All of the active ingredients are indicated for the treatment of athlete's foot as well as the relief of symptoms due to athlete's foot. One active ingredient, tolnaftate, is indicated for the prevention of athlete's foot. In addition, the active ingredients are indicated for the treatment of ringworm (tinea corporis) and jock itch (tinea cruris).

Final Monograph Amendment: "cures most" indication

Following publication of the FM, we published a proposed rule and a final rule on July 22, 1999, and August 29, 2000, respectively, to modify labeling of OTC topical antifungal drug products (Refs. 4 and 5). The amendment added the word "most" to the indication statement between the introductory phrase and the name of the condition(s) for which the product is to be used (e.g., "cures most athlete's foot"). We recognized that OTC topical antifungal drug products do not cure or treat all conditions commonly thought by consumers to be athlete's foot or jock itch. We also noted that varying percentages of subjects were clinically and mycologically cured of athlete's foot infection. Inserting a qualifying word (i.e., "most") into the indication statement would help inform consumers about what they can expect from these products. We pointed out that this amended label is consistent with current labeling approved for OTC vaginal antifungal drug products marketed under NDAs. The OTC vaginal antifungal drug product labeling states that the product "cures most vaginal yeast infections."

Final Monograph Amendment: Addition of clotrimazole as an ingredient

In addition to this amendment, on May 29, 2001, after reviewing approximately seven clinical studies, we proposed to add clotrimazole as a GRASE active ingredient

for the treatment of athlete's foot, jock itch, and ringworm (Ref. 6). On February 8, 2002, we added clotrimazole to the topical antifungal monograph in a final rule.