



APR 21 2005

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Suite 400  
1400 Sixteenth Street, N.W.  
Washington, D.C. 20036-2220

Re: Docket No. 81N-033A/CP1, SUP1, & C75

Dear Ms. Pahl and Dr. Strobos:

This responds to your citizen petition (Petition) dated March 24, 2003, filed as Comment No. CP1, and supplements SUP1, dated May 22, 2003, and C75, dated October 12, 2004, under Docket No. 81N-033A in FDA's Division of Dockets Management (formerly the Dockets Management Branch) on behalf of Sinofresh Research Labs, LLC (Sinofresh). Your Petition specifically requests that FDA take the following actions:

1. Reopen the administrative record for the tentative final monograph (TFM) for over-the-counter (OTC) oral antiseptic drug products (59 FR 6084, February 9, 1994) to allow for submission of additional safety and effectiveness data on cetylpyridinium chloride (CPC) to support the inclusion of 0.025 to 0.1 percent CPC as a Category I (safe and effective) OTC oral/nasal antimicrobial/antiseptic drug product.
2. Include labeling in the TFM for OTC oral antiseptic drug products to allow use of CPC in a nasal spray formulation intended as an oral/nasal antiseptic drug product.

In reaching a decision, FDA has considered all of the information in your Petition and the supplements, the declarations of William Wilferth, R.Ph., M.S., Raymond Fonseca, D.M.D., and Seth Rosenberg, M.D., and other available information. For the reasons described below, your Petition is denied.

## **I. BACKGROUND**

Based on the recommendations of the Advisory Review Panel on OTC Oral Cavity Drug Products (the Panel), FDA published in the Federal Register of May 25, 1982, an advance notice of proposed rulemaking (ANPR) to establish conditions under which OTC oral health care drug products are generally recognized as safe and effective and not misbranded (47 FR 22760). The Panel was charged to evaluate OTC oral health care ingredients for temporary use, which act locally when applied directly to the mucous membranes of the oral cavity (mouth) and pharynx (throat) (47 FR 22760 at 22765).

The Panel concluded that there were insufficient data available (Category III) to permit final classification of the safety and effectiveness of CPC as an OTC antimicrobial active ingredient for this use. Based on the Panel's recommendations and public comment on the ANPR, FDA placed CPC in Category III (insufficient data) in the TFM for OTC oral antiseptic drug products.

## II. DISCUSSION OF ISSUES

### A. Eligibility

The OTC drug monograph system was established to evaluate the safety and effectiveness of all OTC drug products on the market in the United States (U.S.) on or before May 11, 1972, a date that was subsequently extended to December 4, 1975. Your Petition requests the inclusion of labeling in the TFM for OTC oral antiseptic drug products to allow use of CPC in a nasal spray formulation intended as an oral/nasal antiseptic drug product. Your Petition requests certain statements of identity and indications that have no prior OTC marketing history in the U.S., were not considered by the Panel, and that FDA did not propose in the oral antiseptic TFM.

Specifically, your Petition requests that the oral antiseptic TFM include the following labeling:

#### Statements of identity

- Oral antiseptic
- Nasal antiseptic
- Oral antimicrobial
- Nasal antimicrobial

#### Uses

- an aid to daily oral [or nasal] care
- kills germs
- temporarily reduces bacteria in the nose, mouth, and throat
- temporarily reduces fungus in the nose, mouth and throat

#### Directions

- Adults and children 12 years of age and over: Inhale 1-3 sprays in each nostril allowing spray to drain into throat and one spray in mouth. Use daily for up to one month.
- Children under 12 years of age: Consult a doctor.

Your Petition states that the Panel was charged to evaluate oral health care ingredients for use on the mucous membranes of the oral cavity (mouth) and pharynx (throat) (47 FR 22760 at 22765). The Petition notes that the Panel defined the pharynx as including the nasopharynx and contends that the oral health care monograph encompasses OTC nasal antiseptic drug products.

Although the Panel's general discussion of the anatomy and physiology of the oral cavity in the ANPR (47 FR 22760 at 22767) included associated structures such as the nasopharynx, the Panel was charged to evaluate the active ingredients in OTC drug products intended for the temporary relief of symptoms due to minor irritations,

inflammations, and other lesions on the mucous membranes of the oral cavity (mouth) and pharynx (throat). The Panel evaluated ingredients intended to be applied directly to the mucous membranes of the mouth and throat and to act locally (47 FR 22760 at 22765). Thus, the use of a nasal spray as an OTC nasal antiseptic, as described by the Petition, was not considered in the Panel's evaluation of OTC oral antiseptics. Further, the Panel did not review any data on the safety and effectiveness of CPC when used in a spray dosage form as a nasal antiseptic.

In the TFM, FDA defined an oral antiseptic as "a drug product applied topically to the oral cavity to help prevent infection in wounds caused by minor oral irritations, cuts, scrapes, or injury following minor dental procedures" (59 FR 6084 at 6121). FDA's proposal did not include nasal antiseptics. As such, the agency's proposed regulation (TFM) does not provide for oral/nasal antiseptics.

Further, because OTC oral antiseptic drug products are intended only for short term use, FDA proposed the following warning statement for these products: "Do not use for more than 7 days unless directed by a dentist or doctor." Oral antiseptic drug products labeled for long term use of greater than 7 days are not included in the TFM.

The product is not eligible for evaluation in the OTC Drug Review based on its marketing history. FDA is not aware of any U.S. marketing history of CPC in a dosage form intended to be sprayed into the nostrils and labeled as an OTC nasal antiseptic prior to 1975. The Petition does not include documentation that such a product was marketed prior to 1975. For these reasons, FDA considers oral/nasal antiseptics bearing the proposed labeling to be new drugs. Further, marketed products, such as Sinofresh Nasal and Sinus Care Spray, bearing the proposed labeling are unapproved new drugs.

## **B. Effectiveness Data**

Your Petition includes the final reports of two in vitro "Quantitative Mini Kill Time" studies to demonstrate the antimicrobial effectiveness of the Sinofresh Nasal and Sinus Care spray product. The studies used a modification of the methods described in the United States Pharmacopeia (USP) 25 for antimicrobial preservative testing. The studies included positive (sterile water) and negative (not described) microbiological controls.

In one study, samples of the product were inoculated with five American Type Culture Collection (ATCC) strains of test bacteria. Aliquots of the inoculated product were removed at 0 hours (hr), 6 hr, 24 hr, 72 hr, 5 days, and 7 days, and assayed for surviving organisms. In the second study, using a similar protocol, samples of the product were inoculated with six ATCC strains of fungi. Both study reports indicate that none of the organisms showed growth within 72 hours.

These studies have a number of deficiencies, which include the following:

- The studies lack a vehicle control and, therefore, are inadequately designed to demonstrate the contribution of CPC to the antimicrobial activity of the product.
- Only summary data are presented.
- Both studies use a modified USP antimicrobial preservative test without providing a rationale for the modifications.
- The organisms tested are not relevant to the oral cavity, and no rationale is provided for the organisms chosen to be tested.
- The numbers of organisms tested are insufficient to define the spectrum of activity and did not include any fresh isolates.
- Insufficient detail is provided regarding the culture conditions used.
- No rationale is provided for the sampling times used or the concentrations studied.

The Panel proposed specific *in vitro* and *in vivo* testing for reclassifying Category III antimicrobial active ingredients in OTC oral health care drug products for topical use on the mucous membranes of the mouth and throat (47 FR 22760 at 22890). In the TFM, FDA noted the Panel's recommendation that well-designed *in vitro* studies should be required to demonstrate antimicrobial effectiveness. The data obtained from *in vitro* studies should be verified and supported by *in vivo* animal and human studies. FDA agreed with the Panel's conclusion that data from *in vitro* testing alone are insufficient to establish that an oral antiseptic is generally recognized as effective (59 FR 6084 at 6114).

The data presented in your Petition do not meet the guidelines for *in vitro* studies of oral antiseptic drug products recommended by the Panel and are not supported by *in vivo* studies. The remainder of the information included in your Petition regarding the effectiveness of CPC as an oral antiseptic was previously submitted and reviewed by the Panel and FDA. FDA evaluated these data in the TFM and concluded that they are insufficient. Therefore, no new *in vivo* or clinical data are provided that support the effectiveness of CPC as an oral antiseptic.

### **C. Safety Data**

#### **1. Neuromuscular Blocking Effects**

Your Petition includes the declaration of William Wilferth, R.Ph., M.S., regarding the safety of CPC, and a copy of a comment, dated August 3, 1994, submitted by Procter & Gamble in response to the oral antiseptic TFM (Docket No. 81N-033A/C1). Issues discussed in these documents predominantly concern the safety of CPC for use in the oral cavity. The comment noted FDA's concern that use of quaternary ammonium (QA) compounds such as domiphen bromide and CPC in the presence of excessive gum irritation and bleeding could increase the absorption and systemic exposure to the ingredient. This could lead to some of the toxicological effects discussed by the Panel, including neuromuscular blocking of nicotinic and muscarinic receptors. The comment contended that although there are many QA compounds that have cholinergic/antagonist activity, it is inappropriate to conclude that all QA compounds have significant ganglionic or neuromuscular blocking activity. The comment further contended that

there is no experimental basis for suspecting cholinergic agonist/antagonist activity from CPC.

Similarly, the Wilferth declaration discusses safety concerns including cardiovascular and neuromuscular effects. The declaration notes FDA's conclusion in the oral antiseptic TFM that the available data "are sufficient to conclude that CPC is safe as an OTC oral antiseptic when labeled for short-term use (not to exceed 7 days)." The declaration cites safety studies using Sinofresh Nasal and Sinus Care spray containing 0.5 percent CPC and concludes that these studies are consistent with other studies that have evaluated CPC in humans and demonstrate that CPC is safe. However, like the comment discussed above, the declaration does not provide data to support its contention that CPC is safe for long-term use.

## 2. Carcinogenicity

Your Petition also includes declarations by Raymond Fonseca, D.M.D., and Seth Rosenberg, M.D., regarding the possible association between the chronic use of certain mouthrinses and an increased risk of oropharyngeal cancer. The declarations contend that any increased incidence of oropharyngeal cancer that may be associated with chronic overuse of mouthrinses is related to the chronic exposure to high concentrations of alcohol. The declarations contend, therefore, that because Sinofresh Nasal and Sinus Care contains no alcohol, long-term use of this product would not increase the risk of oropharyngeal cancer. However, these declarations provide no data or factual basis for their conclusions.

## 3. Safety of CPC as a Nasal Spray

The data included in the Petition are insufficient to address potential safety concerns relating to the use of CPC on nasal mucosa. The Panel reviewed CPC-containing mouthrinses, which are intended to be expelled, exposing the oral mucosa to CPC for a short time. However, the route of administration of a nasal spray is significantly different than that of a mouthrinse. In contrast, a nasal spray dosage form is not intended to be expelled and may expose the nasal mucosa to CPC for significantly longer time periods. In addition, the nasal delivery of CPC in a spray dosage form raises safety issues regarding potentially adverse bronchial and pulmonary exposure. Thus, a nasal spray dosage form may present unique safety concerns.

Your Petition includes a brief summary of a clinical safety evaluation of Sinofresh Nasal and Sinus Care used as a nasal antiseptic spray. The study involved 24 subjects using the product for an average of 6.8 weeks. This clinical safety evaluation has a number of deficiencies that make it insufficient to support the safety of CPC as a nasal antiseptic. These include the following:

- The study is unblinded.
- The study is not placebo controlled.

- The study involves too few subjects (24), and subjects are predominantly female (19).
- There is no description of how frequently the subjects used the product during the study period, the length of time that each subject participated in the study, or how the subjects were evaluated.

In addition, subjects are described as “healthy with respect to oral/nasal cavity servation” before taking the product and again after a minimum of 4 weeks. The report notes, however, two cases of mild stinging/irritation that the investigators “believed” were attributed to seasonal allergies and allergic rhinitis. The Petition provides no information to support this conclusion.

#### **D. Reopening of the Administrative Record**

The Petition provides little new data to support a request to reopen the administrative record for the rulemaking for OTC oral antiseptic drug products. The evidence provided consists of: (1) Small, inadequately designed studies of the safety and effectiveness of a nasal/oral spray product containing CPC, (2) information previously evaluated by FDA and included in its Category III (insufficient data) determination on the safety and effectiveness of CPC as an oral antiseptic, (3) declarations concerning the potential for neuromuscular blockade of nicotinic and/or muscarinic receptors by CPC and supporting the contention that any increase in oral cancers associated with the chronic overuse of mouthrinses is directly related to chronic exposure to alcohol in these formulations, and (4) new summary information on adverse events reported during clinical testing of CPC-containing oral rinses. Thus, the petition provides an inadequate basis to reopen the administrative record.

### **III. SUMMARY OF CONCLUSIONS**

Based on the above, FDA considers an OTC oral/nasal antiseptic spray product containing 0.5 percent CPC and that is intended for use in the nasopharynx to be an unapproved new drug. As such, it is a product that cannot be legally marketed under the provisions of the OTC oral antiseptic TFM. We are aware of the expansive promotion on the internet of Sinofresh Nasal and Sinus Care that includes claims for the prevention of nasal and sinus symptoms by reducing bacteria and mold in the nasal cavity. Based on the product’s currently labeled claims, the route of administration, and the labeled directions, FDA considers the product to be an unapproved new drug that cannot be marketed without an approved new drug application (NDA).

Further, your Petition provides no new in vivo or clinical data that would support the effectiveness of CPC as an oral/nasal antiseptic. In addition, the clinical safety evaluation included in your Petition has a number of deficiencies that make it insufficient to support the safety of CPC as an oral/nasal antiseptic.

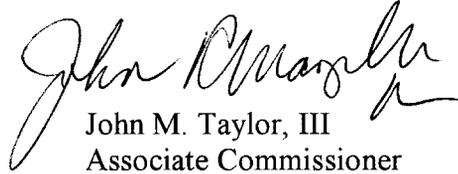
Thus, the information included in your Petition provides an inadequate basis for FDA to reopen the administrative record or to propose to amend the OTC oral antiseptic TFM. Therefore, for the reasons stated above, FDA denies your petition.

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Any comments that you wish to make on the above information should be submitted in triplicate, identified with the docket and comment numbers shown at the beginning of this letter, to the Division of Dockets Management (HFA-305), Food and Drug Administration, 5630 Fishers Lane, Room 1061, Rockville, MD 20852.

Sincerely yours,

A handwritten signature in black ink, appearing to read "John M. Taylor, III". The signature is fluid and cursive, with a prominent initial "J" and a long, sweeping underline.

John M. Taylor, III  
Associate Commissioner  
for Regulatory Affairs