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March 24, 2003

BY HAND DELIVERY

Dockets Management Branch (HFA-305)
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Citizen Petition to Reopen Docket No. 81N-033: Oral Health Care Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Oral Antiseptic Drug Products

Dear Sir or Madam:

Sinofresh Research Labs, LLC (Sinofresh) submits this petition pursuant to 21 C.F.R. § 10.30 requesting that the Food and Drug Administration (FDA) reopen the administrative record to allow for the submission and evaluation of additional data to support the Category I efficacy and safety classification of cetylpyridinium chloride (CPC) in the Oral Health Care Drug Products for Over-the-Counter (OTC) for Human Use Tentative Final Monograph (TFM) for Oral Antiseptic Drug Products, 59 Fed. Reg. 6083 (Feb. 9, 1994). We note from the TFM that no oral antiseptic drug ingredients were found to be Category I for both safety and efficacy. See 59 Fed. Reg. at 6118.

Specifically, in this Citizen's Petition, Sinofresh formally requests that FDA reopen the administrative record to allow for the submission and evaluation of additional efficacy and safety data contained herein that support the Category I safety and efficacy of CPC at concentrations of 0.05 percent.[1] A summary of the efficacy and safety data being submitted is presented below.

[1] Sinofresh believes there is ample data in the docket establishing that CPC up to 0.1% is safe and is effective at 0.025 – 0.1% as an antiseptic. At these concentrations, Sinofresh believes FDA should classify CPC as a Category I for safety and effectiveness in the oral antimicrobial/antiseptic drug monograph. Sinofresh, however, limits this submission to the concentration present in its proposed Sinofresh Nasal Care product, 0.05% CPC.

81N-033A

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I. Data Supporting Efficacy

Sinofresh respectfully submits two final reports of efficacy to the above referenced docket and we request that CPC at concentrations of 0.05 percent be classified as a Category 1 oral antiseptic in the oro- and naso-pharyngeal cavity. The submitted reports provide evidence of substantial antimicrobial efficacy for an oral/nasal spray containing 0.05 percent CPC.

The first study is Protocol No. 200218603-03, Quantitative Mini Kill Time Test. The study was conducted using the pilot Sinofresh Nasal spray product, containing 0.05 percent CPC. The study evaluated survival rate of the following organisms:

Staphylococcus aereus ATCC #6538
Pseudomonas aerunginosa ATCC #9027
Escherichia coli ATCC #8739
Streptococcus pyogenes ATCC#8699
Stachybotrys chartarum ATCC#9182

Effective neutralization of the above organisms was shown.

The second study is Protocol No. 200220302-01, Quantitative Mini Kill Time Test: Fungal. The study was conducted using the pilot Sinofresh Nasal spray product, containing 0.05 percent CPC. The study evaluated survival rate of the following organisms:

Alternaria alternata ATCC #44501
Cladosporium herbarum ATCC #28987
Penicillium funiculosum ATCC #10509
Candida albicans ATCC#10231
Aspergillus niger ATCC#16404
Fusarium solani ATCC#36031

Effective neutralization of the above organisms was shown.

We further attach the following, as demonstration of the efficacy of CPC in concentrations of between 0.025 and 0.1 percent as an antiseptic in the nasopharyngeal cavity.

- August 3, 1994 Letter from Procter & Gamble Company to Dockets Management Branch, FDA, C1, Dkt. No. 81N-033A

- November 26, 1979 submission from Merrell-National Laboratories to Bureau of Drugs, FDA establishing the safety and efficacy of CPC

- November 17, 1982 submission from Procter & Gamble Company to Dockets Management Branch, FDA, C13, Dkt. No. 81N-033A

- November 19, 1982 submission from Merrell Dow Pharmaceuticals Inc. to Dockets Management Branch, FDA, C15, Dkt. No. 81N-033A

II. Data Supporting Safety

In support of the safety of Sinofresh Nasal Care spray, Sinofresh submits the Declaration of William Wilferth, R.Ph., MS. That Declaration summarizes the safety information concerning CPC. Sinofresh Nasal Care spray contains CPC at 0.05% and no alcohol. CPC has been marketed in a mouthwash formulation since 1940 with varying concentrations of alcohol. Studies previously submitted to FDA in Docket No. 81N-0033 plainly establish the safety of CPC.

We also believe that these documents effectively traverse every possible argument that might be made to challenge the safety and efficacy of this formulation.

First, based upon the chemical structure of CPC, FDA had been concerned about the potential for neuromuscular blocking of nicotinic and/or muscarinic receptors. As explained in the Wilferth Declaration, CPC at recommended doses for mouthwash use cannot exhibit such blocking activity. First, CPC does not have the correct chemical structure for such interaction with these receptors. QA's receptor activity is dramatically affected by substituents in the quaternary nitrogen. Additionally, the chemical structure of CPC differs from other QA's in that it has long alkyl chains which place it well out of the range compounds that possess neuropharmacologic activity.

Secondly, as also addressed in the Wilferth Declaration, the lipophilicity from the long alkyl side chains promotes adsorption (binding) to plasma proteins. Protein binding limits the free or pharmacologically active fraction of the drug. Thus, with the intended use as a mouthwash, even if a small amount were absorbed, protein binding would virtually eliminate the possibility of systemic effect. As described below, this binding is also characteristic of alkyl surfactants.

Subsequent research has demonstrated that any cardiovascular and/or neuromuscular effects that do occur with longer linear alkyl chain QA compounds, such as CPC, are a result of interaction of the surfactant with smooth and somatic muscle (and not due to specific receptor mediated effects).

However, any such non-specific surfactant effects require a higher level of active drug at the target site than would be available from CPC used as a mouthwash. Additionally, CPC non-specific surfactant effects are weak; as compared to curare-like drugs (d-tubocurarine and pancuronium), CPC exhibits muscle weakness (via surfactant action) at doses of 2-4 orders of magnitude higher than the muscle paralysis (via receptor mediation) produced by the curare-like drugs. See Wilferth Declaration.

The Sinofresh Nasal Care spray contains 0.05% CPC which translates to a theoretical dose of **0.1400 mg** (assuming a dose of 2 sprays at one time). This dose is orders of magnitude below the dose needed to see an effect since it has been shown that iv doses of approximately **20-100 mg/kg** of CPC are required to produce muscle weakness. Clearly, even if the dose were completely absorbed, which is highly unlikely, only a small fraction of the dose administered to the nasal cavity would be pharmacologically active.

The Wilferth Declaration also summarizes safety information gathered on the Sinofresh Nasal Care product specifically. Sinofresh provided two ear-nose-throat physicians with Sinofresh Nasal Care product which were, in turn, administered to adult patients (over 20 yrs of age) for a mean period of 6.8 weeks or longer than the recommended administration. The physicians prospectively evaluated each of these patients for any potential side affects or adverse reactions. The patients were noted to be healthy with respect to oral/nasal cavity observation before taking the product and again after a minimum of 4 weeks of use. In addition, patients were asked if they noticed anything that may constitute a side effect or adverse drug reaction.

A total of 24 patients received product samples. The patients were an average age of 32 years. There were 19 females and 5 males. Average duration of exposure was 6.8 weeks. Two reports of mild stinging/irritation were noted. Both were transient and self-limited. The physicians believed the effects were due to seasonal allergies and allergic rhinitis. Both events resolved spontaneously.

Sinofresh also submits a declaration from Dr. Seth Rosenberg addressing the concerns raised by the Panel for the Review of Over-the-Counter Oral Cavity Drug Products (the Panel) on August 14, 1979. During that meeting the Panel discussed the safety and efficacy of certain quaternary ammonium compounds that bear an antimicrobial claim for use on the oral and pharyngeal mucous membranes and the arguments and theories emerging from reports such as those contained within Weaver, A. et al. Mouthwash and oral cancer: carcinogen or coincidence? J. Oral Surg. 37:250-253 (1979) Specifically, Weaver, et al. and the Panel hypothesized a link between the chronic overuse of certain mouthwashes containing alcohol and an increased risk of oral/pharyngeal cancers in those patients without other exposure to alcohol.

In the intervening 24 years, additional data on risk factors associated with squamous cell cancer of the oropharynx has been developed. It is the prevailing medical view, as set forth in

the enclosed Declaration, that to the extent there is any increased incidence of oral/pharyngeal cancers that may be associated with chronic overuse of mouthwashes containing alcohol, such incidence is directly related, as set forth in the Weaver article, to the chronic exposure to alcohol and is unrelated to any other ingredients contained therein. Sinofresh intends to submit additional declarations addressing this issue further. [The SinoFresh product contains no alcohol.]

Specifically, there are neither indications nor data that daily use of quaternary ammonium compounds such as CPC for the period recommended creates risk of cancer in the absence of alcohol exposure.

FDA itself has reviewed data about a relationship between long-term mouthwash use and increased risk of oral and pharyngeal cancers. The agency similarly was of the view that any increased incidence of oral/pharyngeal cancers that may be associated with chronic overuse of mouthwashes was related to the chronic exposure to alcohol. As a consequence, the agency recommends that alcohol be included in OTC oral health care drug products only to the extent necessary to dissolve the active ingredient(s). 59 Fed. Reg. 6084, 6090 (Feb. 9, 1994).

III. Oral/Nasal Dosage

Sinofresh makes this submission for its oral/nasal antiseptic product. The product, as discussed above, containing 0.05% CPC as an active ingredient, delivers approximately 0.1400 mg per dose to the mucosa. We believe the oral health care drug products monograph encompasses this oral/nasal product.

We note that in the 1982 findings of the Advisory Review Panel on OTC Oral Cavity Drug Products (47 Fed. Reg. 22760 (May 25, 1982)), the Panel was charged with evaluating ingredients in OTC preparations used for oral health care. "These ingredients are intended to be used for the temporary relief of symptoms due to minor irritations, inflammations, and other lesions on the mucous membrances [sic] of the oral cavity (mouth) and pharynx (throat)." 47 Fed. Reg. at 22765. The Panel defined the "pharynx (throat)" as including the nasopharynx,[2] the oropharynx, and laryngopharynx.[3]

More generally, the Panel itself determined that "oral cavity" monograph products should be recast as the "oral health care products." "The Panel concluded that 'oral health care' would

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[2] "Nose drops, sprays, and other OTC preparations instilled into the nose pass into the pharynx and may exert a therapeutic effect in some cases and an adverse effect in others." 47 Fed. Reg. at 22778.

[3] See proposed Definitions, II.A.22(a)-(c), 47 Fed. Reg. at 22764-22765.

be a more appropriate term to describe the function of these products to the lay public." 47 Fed. Reg. at 22762. The Panel came to this conclusion because of exposure of these drug products not just to the mouth, but to "associated structures" of the mouth, such as mucosa and glands that are not strictly within the oral cavity itself.[4] To that end, the proposed definition of "oral cavity" itself included the palate and organs whose ducts open into the oral cavity.

In any event, the Panel evaluated ingredients' effects upon the mucous membranes of the oral cavity (mouth) and oro- as well as naso-pharynx (throat). 47 Fed. Reg. at 22765. The proposed product submitted by Sinofresh is on all fours with the scope of the monograph since the proposed labeling recommends use throughout these anatomic structures.

IV. Proposed Actions

Sinofresh requests that FDA take the following actions:

1. Identify cetylpyridinium chloride up to 0.1% for safety and at 0.025 – 0.1% for effectiveness as a Category I monograph oral antimicrobial/antiseptic drug.

2. Approve the following statements of identity:

    a. Oral Antiseptic
    b. Nasal Antiseptic
    c. Oral Antimicrobial
    d. Nasal Antimicrobial

3. Authorize use of the following label indications/claims, and any similar statements for a 0.05 percent cetylpyridinium chloride-containing product for the nasopharyngeal cavity:

    a. An aid to daily oral [or nasal] care
    b. Kills germs
    c. Temporarily reduces bacteria in the nose, mouth, and throat
    d. Temporarily reduces fungus in the nose, mouth, and throat

[4] "Oral cavity" was proposed to be defined as "The cavity of the mouth and associated structures, including the cheeks, palate, oral mucosa, glands whose ducts open into it, the teeth, and the tongue." 47 Fed. Reg. at 22764.

4. Authorize use of the following directions for use:

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

V. Environmental Impact

This petition qualifies for a categorical exemption from the requirement of submission of an environmental assessment. 21 C.F.R. § 25.31(c).

VI. Economic Impact

The petitioner need only submit information on economic impact upon request of the Commissioner. 21 C.F.R. § 10.30(b).

VII. Certification

The undersigned certifies that, to the best of his knowledge and belief, this petition includes all information and views on which the petition relies, and that it includes representative data known to the petitioner that are unfavorable to the petition.

* * *

Until FDA acts upon this Petition by re-opening the docket for consideration of additional data, Sinofresh asks that the Protocol No. 200218603-03, Quantitative Mini Kill Time Test and Protocol No. 200220302-01, Quantitative Mini Kill Time Test: Fungal remain confidential.

Please contact me with any questions regarding this submission.

Sincerely,

Tish E. Pahl
Jur T. Strobos, M.D.
Counsel to Sinofresh Research Labs, LLC

OFW:dah
Attachments

ATTACHMENTS AND REFERENCES

Protocol No. 200218603-03, Quantitative Mini Kill Time Test

Protocol No. 200220302-01, Quantitative Mini Kill Time Test: Fungal

Declaration of William Wilferth R.Ph., MS

August 3, 1994 Letter from Procter & Gamble Company to Dockets Management Branch, FDA, C1, Dkt. No. 81N-033A

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November 19, 1982 submission from Merrell Dow Pharmaceuticals Inc. to Dockets Management Branch, FDA, C15, Dkt. No. 81N-033

Robinson, R.F. The effect of quaternary ammonium compounds on oral bacteria: An *in vivo* study using cetylpyridinium chloride. J. Dent. Ass. S. Afr. 25:68-74, 1970.

Weaver, A. et al. Mouthwash and oral cancer: carcinogen or coincidence? J. Oral Surg. 37:250-253, 1979.

Declaration of Seth Rosenberg, M.D.