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

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

Dear Sir or Madam:

We submit these comments in response to the citizen petition of Sinofresh Research Labs, LLC (Sinofresh) to reopen Docket No. 81N-033A, the Tentative Final Monograph (TFM) for Oral Antiseptic Drug Products.[1] Sinofresh seeks to reopen the administrative record of this TFM so that it may submit additional data to support the classification of 0.05% cetylpyridium chloride (CPC) as Category I for safety and effectiveness. CPC is currently Category III for oral antiseptic use because available data are insufficient to classify the ingredient safe and effective and further testing is required.

The citizen petition and data submitted by Sinofresh do not support the reclassification of CPC from Category III to Category I for oral antiseptic use. Sinofresh unsuccessfully attempts to include a *nasal* spray in a monograph for *oral* health care products and consequently expand the parameters of this TFM to include a product with different indications for use, a different route of administration, and a different exposure time in the body. Sinofresh has failed to meet the clear testing and data standards previously set by FDA, and its submission leaves unresolved significant issues regarding effectiveness. Potentially serious safety concerns relating to the use of CPC on nasal cilia and mucosa may exist, and Sinofresh

[1] 59 Fed. Reg. 6084 (Feb. 9, 1994).

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has submitted no data to address these concerns. Sinofresh has thus not established good grounds to reopen the administrative record of the TFM.

I. Background

A. History of the Oral Antiseptic Drug Products TFM

In crafting the oral antiseptic TFM at issue, FDA carefully considered the safety and effectiveness of CPC on several occasions and presented a clear path by which to expand the parameters of the monograph. In 1982, the Advisory Review Panel on Over-the-Counter (OTC) Oral Cavity Drug Products (the Panel) issued an advance notice of proposed rulemaking establishing the conditions under which OTC oral health care drug products are generally recognized as safe and effective and not misbranded.[2] The Panel reviewed CPC as an OTC antimicrobial for topical use on the mucous membranes of the mouth and throat. It noted that CPC is a quaternary nitrogenous compound derived from pyridine. The Panel expressed concern that toxic doses of CPC exhibit systemic effects, such as an autonomic (nicotinic) blocking effect on the ganglia and a curariform (muscarinic) response.[3] The Panel concluded that insufficient data existed on CPC's tumorigenic, mutagenic, and teratogenic effects in humans during long-term use, and therefore, it classified CPC in Category III for safety.[4]

With respect to the effectiveness of CPC, the Panel again classified CPC in Category III. The Panel noted that "there are no data to justify the use of [CPC] in oral health care products on a continuing day-to-day basis for protracted periods of time for prophylaxis and other uses when no symptoms are present and no therapeutic benefit can be demonstrated."[5] It concluded that proof of CPC's ability to kill or inhibit certain microorganisms found in the mouth is insufficient to demonstrate a therapeutic benefit in treatment of sore mouth or throat.[6]

Because this classification was made in an advance notice of proposed rulemaking, the Panel suggested experimental protocols that might be employed to support an upgrade of an oral antiseptic ingredient from Category III to Category I for safety and effectiveness in the final monograph.[7] As discussed in further detail below, the

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[2] 47 Fed. Reg. 22760 (May 25, 1982).

[3] *Id.* at 22865; *see also* 22846-47.

[4] *Id.* at 22865.

[5] *Id.* at 22866.

[6] *Id.*

[7] *Id.* at 22890-93. The Panel did not classify any oral antiseptic drug ingredients in Category I.

recommendations included both *in vitro* and *in vivo* testing. The Panel expected that the test results demonstrate "that preparations applied to the mucous membranes of the mouth and throat act topically and reduce pathogenic microbial populations to levels that are therapeutic and that relieve symptoms caused by the infection."[8]

In 1994, FDA issued the Tentative Final Monograph for Oral Antiseptic Drug Products (the monograph that Sinofresh is requesting be reopened).[9] FDA defined an oral antiseptic as "[a]n antiseptic-containing 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."[10] It approved a variety of indications for use, including "First aid to help prevent infection in minor oral irritation caused by accidental injury."[11]

FDA examined CPC for use as an oral antiseptic and addressed the comments it had received in response to the advance notice of proposed rulemaking. It noted the distinction between products recommended for long-term use, like mouthwash, and products intended for short-term use, and stated that safety concerns regarding the long-term use of oral antiseptic ingredients were not necessarily relevant to the short-term use of these ingredients. FDA reviewed several CPC toxicity studies and adverse reaction files. It concluded that 0.025 to 0.1% CPC is safe as an OTC oral antiseptic when labeled for short-term use (*i.e.*, use is not to exceed seven days).[12] However, FDA noted its continuing concern regarding CPC's potential toxicological effects discussed by the Oral Cavity Panel, especially in situations in which excessive gum irritation or bleeding exists, and recommended product labeling to warn consumers against use in such situations.

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[8] *Id.* at 22890.

[9] 59 Fed. Reg. 6084 (Feb. 9, 1994). FDA issued TFMs for OTC oral health care drug products in several segments. The first segment, published in 1988, covered anesthetic/analgesic, astringent, debriding agent/oral wound cleanser and demulcent drug products. 53 Fed. Reg. 2436 (Jan. 27, 1988). The second segment included relief of oral discomfort drug products. 56 Fed. Reg. 48302 (Sept. 24, 1991). The TFM for oral antiseptic drug products was the third segment published. Another part of the oral health care drug product scheme involves antiplaque and antiplaque related products. FDA published a call for data for OTC antiplaque ingredients, and then published an advance notice of proposed rulemaking based on the Plaque Subcommittee of the Nonprescription Drugs Advisory Committee (the Subcommittee) review of the submissions. 68 Fed. Reg. 32232 (May 29, 2003).

[10] 59 Fed. Reg. at 6104-05.

[11] *Id.* at 6121-22.

[12] *Id.* at 6094.

With respect to effectiveness issues, FDA continued to classify CPC in Category III.[13] FDA received many reports of *in vitro* and *in vivo* studies conducted to demonstrate the effectiveness of CPC as an antiseptic agent. However, many of these studies failed to follow the Panel's recommended experimental protocols.[14] For example, in one study, the incubation conditions used to prepare the test cultures were unlike those recommended by the Panel. In another study, CPC alone was not tested, making it impossible to determine whether or not CPC was effective in reducing the bacterial population of the oral cavity. Other studies were based upon plaque reduction, which both the Panel and FDA agreed was not an appropriate criterion for determining the effectiveness of oral antiseptics. Finally, FDA noted that it was "not aware of any data from clinical studies demonstrating a therapeutic benefit from the OTC use of [CPC] as an antiseptic in the oral cavity."[15]

FDA concluded that additional data were still necessary "to establish the effectiveness of [CPC] as an oral antiseptic to help prevent infection in the oral cavity." It stated that the Panel's proposed *in vitro* and *in vivo* guidelines represented "a good starting point for the design of studies to upgrade . . . a Category III oral antiseptic ingredient to Category I."[16] FDA proposed additional *in vivo* testing considerations, including a stipulation of "the specific organisms to be tested, the acceptable decrease in bacterial numbers, and the period of time for which the antiseptic activity should persist." FDA also modified the sampling time intervals after treatment with the oral antiseptic.[17] Additionally, FDA concluded that final formulation testing of oral health care antiseptic products was necessary and proposed final formulation testing procedures to include in the TFM.[18]

At no point in crafting the TFM at issue did FDA consider the nasal use of CPC. All of its review and consideration was limited to CPC's effect on the oral cavity.

B. Accepted Uses of CPC

In its OTC monograph review, FDA has accepted the use of CPC in a drug in only one specific and limited circumstance. In May 2003, FDA issued an advance notice of proposed rulemaking for OTC drug products for the reduction or prevention of dental plaque and

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[13] *Id.* at 6095, 6118.

[14] *Id.* at 6095.

[15] *Id.*

[16] *Id.* at 6095, 6114-15.

[17] *Id.* at 6114-15.

[18] *Id.* at 6119.

gingivitis.[19] The Subcommittee, after its review of the submissions in response to FDA's call for data for OTC antiplaque ingredients, concluded that CPC at concentrations of 0.045 to 0.1% with at least 72 to 77% chemically available CPC "is safe and effective for use in mouthrinse formulations as an OTC antigingivitis/antiplaque agent."[20] With respect to safety concerns, the Subcommittee addressed the teratogenic and mutagenic concerns raised by FDA in the TFM for oral antiseptic products and noted that although long-term cumulative effects on metabolism and teratogenic effects were not available from controlled human studies, "clinical experience following long-term OTC use of the ingredient has not revealed overt toxic manifestations."[21] With respect to effectiveness concerns, the Subcommittee reviewed six clinical trials and concluded that based on the totality of the data, CPC is effective as an antigingivitis/antiplaque ingredient within the dosage limits described above.[22]

This use of CPC in an oral mouthrinse for gingivitis and plaque is the sole drug use FDA has accepted to date for the ingredient.[23] FDA has never approved CPC for use in a nasal spray or any other nasal product.

C. Sinofresh Request

Sinofresh seeks to expand the TFM for oral antiseptic products to include 0.05% CPC for use in a nasal antiseptic spray. Sinofresh is a Florida company that advertises itself as a leader in the field of "chronic sinus distress." (Attachment 1) Notwithstanding its pending petition, the company already manufactures and markets "Antiseptic SinoFresh" as a nasal and sinus spray, apparently outside the TFM or any other current monograph, and without any FDA approval. (Attachment 2) According to the product packaging, SinoFresh is a "patented nasal, oral & sinus product" that "clears nasal passages," is "clinically proven," and is "non addictive." (Attachment 2) The Drug Facts panel on the product states that its active ingredient is 0.05% CPC (Attachment 2), and the citizen petition (p. 4) further indicates that drug is delivered to the nasal mucosa at a concentration of 0.14 milligram per dose.

The product Drug Facts panel lists two uses: (1) "kills germs and bacteria," and (2) "reduces germs and bacteria in the nasal passages." (Attachment 2) The Company promotes

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[19] 68 Fed. Reg. 32232 (May 29, 2003).

[20] *Id.* at 32247.

[21] *Id.* at 32248.

[22] *Id.*

[23] Outside the drug context, FDA recently amended the food additive regulations to provide for the use of CPC as an antimicrobial agent in poultry processing. 69 Fed. Reg. 17297 (April 2, 2004).

SinoFresh (purportedly a "revolutionary product" that attacks the molds and bacteria in the nose) for a far broader set of uses. (Attachments 2 & 3) In particular, the Company claims in promotional materials that SinoFresh kills molds and bacteria on contact, moisturizes and refreshes the nasal membranes, fights odor-causing bacteria known to cause bad breath, relieves sinus allergies, and eliminates nasal obstructions resulting from excess mucous matter. (Id.) In radio commercials, spokespersons compare SinoFresh to other OTC nasal sprays such as Afrin® (oxymetazoline HCl 0.05%) and Dristan® (oxymetazoline hcl 0.05%). Both are nasal decongestant products. (Attachment 4)[24]

II. Discussion

A. SinoFresh Nasal Spray Does Not Fall Under the Oral Antiseptic TFM.

Safety and effectiveness considerations aside, the SinoFresh product -- a *nasal* spray -- does not fit within the parameters of the *oral* antiseptic TFM. In the advance notice of proposed rulemaking, the Panel defined oral health care as "[t]he proper care of the mouth, including the temporary relief of symptoms of the mouth and throat, for example, occasional minor sore throat or mouth soreness."[25] Additionally, as mentioned above, FDA's definition of oral antiseptic is a product that prevents infection in wounds caused by minor oral irritations, cuts, scrapes, or injury following minor dental procedures. Sinofresh describes its product as an oral/nasal antiseptic product. However, the product is a nasal spray and the focus of its promoted indications are nasal maladies (*e.g.*, nasal congestion and sinus allergies). The product thus falls outside this monograph.

Sinofresh unsuccessfully attempts to stretch the Panel's definition of "oral cavity" to include the nose by arguing that the nose is an "associated structure" of the mouth. The Panel defined "oral cavity" as "[t]he cavity of the mouth and associated structures, including the cheeks, palate, oral mucosa, glands whose ducts open into it, the teeth, and the tongue."[26] The definition does not include the nose and does not appear to contemplate the inclusion of the nose as an associated structure. While the Panel recognized that the mouth and throat are continuous with other systems of the body, such as the lower respiratory and gastrointestinal tract, it limited

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[24] According to the Sinofresh website (http://www.sinofresh.com), antiseptic Sinofresh is marketed to the six top drug/food chains nationally (CVS, Eckerd, Walgreen's, Publix, Rite Aid, Osco/Sav-On). It is marketed as a nasal spray and is usually located in an entirely different location from the oral care section.

[25] 47 Fed. Reg. at 22764.

[26] *Id.*

its consideration to the effect that ingredients exert on the mucous membranes of the mouth and throat.[27]

SinoFresh's advertised indications for use as a nasal decongestant and sinus allergy reliever appear to place it more appropriately under the Cold, Cough, Allergy, Bronchodilator, and Antiasthmatic Drug Products for Over-the Counter Human Use monograph.[28] This monograph covers a wide range of indications for use, including "Temporarily relieves nasal congestion associated with sinusitis" and "Promotes nasal and/or sinus drainage; temporarily relieves sinus congestion and pressure."[29] This monograph, however, does not recognize CPC, the active ingredient of SinoFresh, as safe and effective for any of the indicated uses.

Sinofresh could potentially seek to add CPC to the cough cold monograph. For present purposes, however, what is clear is that its petition to include a CPC *nasal* spray within the *oral* antiseptic TFM is misplaced.

B. SinoFresh has Not Demonstrated the Effectiveness of CPC for its Claimed Uses.

The Panel and FDA have presented clear guidelines by which to structure *in vitro* and *in vivo* studies to support the reclassification of an oral antiseptic ingredient from Category III to Category I for effectiveness. These guidelines do not describe the way in which a nasal antiseptic ingredient fits under an oral health care product monograph. Notwithstanding the above, Sinofresh submitted two studies purporting to demonstrate the neutralization of certain mold, bacteria, and fungi organisms by 0.05% CPC. Neither of these studies fulfills the guidelines FDA previously set down.

For example, with respect to the *in vitro* test guidelines, the Panel recommended that the test measure the effectiveness of the antiseptic ingredient at killing test organisms within the first two minutes of exposure. According to the Panel, the two-minute exposure time reflects the contact time of the product *in vivo* before it is diluted by oral fluids.[30] The test methods used in the studies submitted by Sinofresh measured ingredient activity at 0, 6, 24, and 72 hours, and 5 and 7 days. The test organisms used in the Sinofresh studies were unlike those recommended by the Panel, and some of the culture conditions were not specified (*e.g.*, how the cultures were

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[27] *Id.* at 22766.

[28] 21 C.F.R. § 341.

[29] 21 C.F.R. § 341.80(b)(1) and (2)(v).

[30] 47 Fed. Reg. at 22891.

grown, aerobically or anaerobically). Additionally, the Panel recommended that the test be conducted in the presence of biological fluids, specifically sterile fetal calf serum, and neither Sinofresh study included this variable.

Even if Sinofresh's petition contained adequate *in vitro* data -- which it does not -- the petition would be lacking because it contains no *in vivo* testing to establish the effectiveness of CPC as an oral antiseptic. The Panel required both *in vitro* and *in vivo* test data, and recommended that *in vivo* test methods "be designed to closely approximate the clinical situations for which a product is intended to be used and to substantiate claims in the labeling that the relief of symptoms of mouth and throat infections is indeed due to an antimicrobial activity of an ingredient."[31] In the TFM, FDA noted its belief that "data from in vitro testing alone are insufficient to establish that an oral antiseptic is generally recognized as effective," and proposed *in vivo* testing guidelines in addition to the ones described by the Panel in the advance notice of proposed rulemaking.[32] The two limited *in vitro* studies submitted by Sinofresh are insufficient to demonstrate the effectiveness of CPC for human use, let alone to substantiate the wide range of clinical benefits the company is claiming that SinoFresh provides.

In addition to proposing *in vivo* guidelines, FDA concluded that final formulation testing of OTC oral antiseptic drug products is necessary because the final formulation can influence the effectiveness of the active ingredient.[33] In the TFM, the proposed final formulation testing procedures required evidence that the active ingredient at the lowest recommended use concentration decrease the number of bacteria per milliliter by 3 $\log_{10}$ within 10 minutes at 37°C in the presence of 10% serum *in vitro*.[34] Sinofresh submitted no data from final formulation testing.

None of the data or materials submitted by Sinofresh demonstrates that using the SinoFresh spray provides any therapeutic benefit to the user. As discussed above, Sinofresh submitted just two *in vitro* studies purporting to demonstrate the elimination of various bacteria, mold, and fungi by CPC. These *in vitro* tests failed to comport with FDA's establishing testing methodology. Further, the tests do not begin to address clinical benefit. Nowhere in the petition

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[31] *Id.*

[32] 59 Fed. Reg. at 6114. This conclusion reflects FDA's general view that "[*i*]*n vitro* microbiologic data establish *in vitro* microbiologic *activity* only." See Letter to Application Holders from Lillian Gavrilovich, MD, Acting Director, Division of Anti-Infective Drug Products, and Janet L. Rose, Director, Division of Drug Marketing, Advertising and Communications, FDA re: "Anti-Infective Promotion" at 1 (September 1994).

[33] 59 Fed. Reg. at 6119.

[34] *Id.* at 6122-24 (to be codified at 21 C.F.R. § 356.90).

is there an explanation (let alone supporting data) for how eliminating bacteria, mold, and fungi from the nose clears sinuses, relieves nasal congestion, eliminates bad breath, or provides any other benefit. FDA has repeatedly stressed the importance of demonstrating such clinical benefit.

In the proposed rule, the Panel expressed skepticism that oral antiseptic products provide any benefit at all. It noted that the oral cavity is endowed with physiologic mechanisms for maintaining the healthy state of structures contained therein and that no medicines are necessary to achieve this end.[35] In the TFM, one of the reasons FDA classified CPC in Category III was because no data from clinical studies demonstrated a therapeutic benefit from the OTC use of CPC as an antiseptic in the oral cavity.[36] The Sinofresh petition does little to meet this need for data.

C. Safety Concerns Remain for CPC, Particularly with Nasal Administration

As noted above, the Subcommittee's conclusion that CPC at concentrations of 0.045 to 0.1% with at least 72 to 77 percent chemically available CPC is safe for use was specifically based on use in mouthrinse formulations as an OTC antigingivitis/antiplaque agent.[37] This finding does not consider the use of CPC in a nasal spray and leaves open a number of safety concerns for the Sinofresh product. The modes of administration of a mouthrinse solution and a nasal spray are significantly different and potentially present unique safety considerations. Additionally, Sinofresh's marketed indications present further potential safety issues that have not been addressed by FDA or its advisory panels.

As to the open safety issues for nasally delivered CPC, the effect of CPC on nasal cilia and mucosa may be different than its effect on oral cavity tissues. The Subcommittee limited its review of CPC to mouthrinse products, during the use of which CPC is in limited contact with the oral mucosa and the product is to be expelled after brief exposure. In contrast, nasal sprays are not designed to be expelled, and consequently, the nasal mucosa are exposed to CPC for much longer periods of time. CPC's effect on the oral mucosa and associated structures does not establish its effect on the nasal cilia and mucosa because of the physiological differences between the two structures.

FDA, in the Final Monograph for OTC Nasal Decongestant Drug Products, noted the sensitivity of the nasal cilia and mucosa and concluded that studies that examined oral or

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[35] 47 Fed. Reg. at 22766.

[36] 59 Fed. Reg. at 6095.

[37] 68 Fed. Reg. 32232, 32247.

injectable routes of administration were not useful to evaluate topical effects of nasal decongestants.[38] FDA found in particular that "[m]any drugs . . . are absorbed well from the mucosa of the oropharynx and can be more rapidly and completely absorbed than when ingested orally."[39] Additionally, FDA noted its concern that the recommended dosage of the different applications varies and therefore, drawing conclusions for topical nasal decongestants from an oral nasal decongestant study is difficult.[40] Sinofresh has submitted no evidence to address these concerns and demonstrate that the safety conclusions relating to CPC in mouthrinses drawn by the Subcommittee are applicable to CPC in nasal sprays.

An additional safety concern that arises from the nasal delivery of CPC in a spray mist is potentially adverse bronchial and pulmonary exposure. The mode of administration of a mouthrinse does not lead to bronchial or pulmonary exposure, and the Subcommittee did not consider the possibility of this exposure. The nasal spray application raises this risk, however, and the Sinofresh petition lacks evidence demonstrating that CPC is safe for exposure to these areas.

Separate and apart from the open safety issues related to nasal administration of CPC are safety concerns related to Sinofresh's marketed indications in the OTC setting. The presence of nasal mold and bacteria may indicate a nasal infection that is only properly treated with a topical prescription antibiotic or systemic antibiotic. These infections require diagnosis and treatment by a learned intermediary. When left untreated, nasal infections can readily progress to cellulitis, a potentially serious condition. The product labeling and indications for use present on the Sinofresh packing and on its website specify self-administration and thus risk inappropriate treatment of these potentially serious nasal infections. The Sinofresh petition offers no data to establish that its product can be used safely in an OTC setting in light of this potential for patient misdiagnosis and mistreatment.

Additionally, the role of bacteria and mold in sinus congestion has not been established (other than in sinus infections). Use of a nasal antiseptic spray may cause more harm than benefit because such sprays could alter the normal nasal flora and potentially lead to an overgrowth of more significant microorganisms, such as staphylococcus. This alteration of nasal flora may potentially alter the nose's natural defenses. Sinofresh also offers no data on this additional important safety consideration.

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[38] 59 Fed. Reg. 43386, 43402 (Aug. 23, 1994).

[39] *Id.*

[40] *Id.*

D. There is No Support for Sinofresh's Requested Statements of Identity and Label Indications.

Sinofresh has failed to establish that CPC should be added to the oral antiseptic TFM as a Category 1 ingredient for safety and effectiveness. Even if CPC were added to the TFM, however, there would not be a basis to adopt the overly broad statements of identity and labeling indications that Sinofresh has proposed.

Sinofresh requests that FDA approve the following statements of identity: oral antiseptic, nasal antiseptic, oral antimicrobial, and nasal antimicrobial. In the TFM, FDA concluded that the term "oral antiseptic" is appropriate as the statement of identity for oral health care antiseptics.[41] FDA did not include "oral antimicrobial" as an alternate statement of identity, and Sinofresh does not offer a basis for doing so now.[42] Sinofresh's request to equate nasal and oral is similarly unsupported, and runs directly contrary to FDA's prior treatment of what constitutes an associated structure of the mouth, as addressed above.

Sinofresh also requests that FDA authorize use of the following labeling indications/claims: an aid to daily oral [or nasal] care; kills germs; temporarily reduces bacteria in the nose, mouth, and throat; and temporarily reduces fungus in the nose, mouth, and throat. FDA has specifically considered and rejected such claims in its prior reviews. In the TFM, FDA explicitly concluded that claims such as "an aid to daily oral [or nasal] care" are not appropriate drug claims.[43] FDA similarly determined that the labeling claim "temporarily reduces bacteria in the mouth and throat" is not an appropriate indication for OTC oral health care drug products, because it does not inform consumers "of what benefit might be expected to result from reducing the bacteria in the mouth and throat. Furthermore, the agency is not aware of any data demonstrating that reducing the bacteria in throat has a therapeutic benefit."[44] These concerns also establish the inappropriateness of Sinofresh's labeling claim "temporarily reduces fungus in the nose, mouth, and throat."

III. Conclusion

Sinofresh's citizen petition should be denied. Sinofresh seeks inappropriately to stretch a tentative final monograph for oral antiseptic drug products to cover a product with a different route of administration, different indications, and different exposure considerations.

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[41] *Id.* at 6105.

[42] *Id.*

[43] *Id.* at 6108.

[44] *Id.* at 6107.

The petition does not begin to provide the type or quantity of data that are needed to support a nasal CPC spray for the wide range of claimed indications for which Sinofresh already markets the product. Substantial open safety and effectiveness issues remain open. Accordingly, there is not a basis to reclassify CPC from Category III to Category I.

Respectfully submitted,

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Affairs

Enclosures