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April 30, 2012

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061
Rockville, MD 20852

CITIZEN PETITION

The undersigned, Colgate-Palmolive Company ("Colgate"), submits this Citizen Petition ("Petition") under Section 505 of the Federal Food, Drug, and Cosmetic Act (FDCA) and 21 C.F.R. §10.30 to request the Agency to permit the marketing of a dentifrice toothpaste containing the following active ingredients: Sodium Monofluorophosphate 1.14% (1500 ppm, 0.20% w/v fluoride ion), Potassium Nitrate 5%, and Zinc Citrate 2%, on the basis that this combination is generally recognized as safe and effective for over-the-counter ("OTC") use.

In this case, the review of Sodium Monofluorophosphate for Anticaries is final, and there is a proposed Category I status on safety and efficacy for Postassium Nitrate for Hypersensitivity Pain Relief. FDA has recognized Zinc Citrate as safe in the Antigingivitis/Antiplaque TFM, and with this Petition, Colgate confirms Zinc Citrate's safe and effective use for Antigingivitis/Antiplaque. Moreover, FDA has acknowledged that the combination of Sodium Monophosphate and Potassium Nitrate is acceptable as an Anticaries/Antisensitivity combination, and indeed has long been marketed widely as such in the US. Through this Petition, Colgate now establishes that the addition of Zinc Citrate to the acknowledged combination results in a rational, safe and effective product indicated for Anticaries, Hypersensitivity Pain Relief, and Antigingivitis/Antiplaque.

A. ACTION REQUESTED

Colgate requests that during the process to amend the applicable rulemaking, FDA issue a notice of enforcement policy permitting the interim marketing of the combination before a Final Amendment is published, as it did with Potassium

FDA-1981-N-0015 CP

Nitrate and Fluoride in 1992.[1] Colgate proposes specific language below and also requests that the Agency amend the Oral Health Care Drug Products for Over-the-Counter Human Use; Amendment to Tentative Final Monograph to Include OTC Relief of Oral Discomfort Drug Products; Notice of Proposed Rulemaking (56 Fed. Reg. 48,302, Sept. 24, 1991) ("Oral Discomfort TFM") (Docket No. 81N-0033) to allow the marketing of a dentifrice ("toothpaste") containing a combination of Sodium Monofluorophosphate 1.14%, Potassium Nitrate 5%, and Zinc Citrate 2% for the benefits of Anticaries, Hypersensitivity Pain Relief, and Antigingivitis/Antiplaque, respectively. Accordingly, Colgate submits this Petition to Docket No. 81N-0033.

As background, we identify the rulemaking status of the three ingredients in the proposed formulation:

> *Sodium monofluorophosphate* is included in the Anticaries Drug Products for Over-the-Counter Human Use; Final Monograph (60 Fed. Reg. 52,474, Oct. 6, 1995) (21 CFR § 355) ("Anticaries Monograph") (Docket No. 80N-0042).
>
> *Potassium nitrate* is included in the Oral Discomfort TFM.
>
> *Zinc Citrate* is Category I for safety and Category III for efficacy as an antigingivitis/antiplaque active ingredient under the Oral Health Care Drug Products for Over the-Counter Human Use; Antigingivitis/Antiplaque Drug Products; Establishment of a Monograph; Proposed Rules - Advance Notice of Proposed Rulemaking (68 Fed. Reg. 32,232, May 29, 2003) ("Antigingivitis/Antiplaque ANPR") (Docket No. 81N-0033). Additional studies conducted by Colgate confirming both safety and efficacy of zinc citrate for Antigingivitis/Antiplaque are provided with this Petition.

Granting this Petition would entail amending the Oral Discomfort TFM and Antigingivitis/Antiplaque ANPR as noted below in boldface type:

> Oral Discomfort TFM:
>
> § 355.26 Permitted combinations of active ingredients.
>
> . . . . .
>
> (h) Potassium nitrate identified in § 356.22 may be combined with any single Anticaries active ingredient identified in § 355.10(a) **and**

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any single Antigingivitis/Antiplaque active ingredient identified in § 356.15(f) of this chapter.

Antigingivitis/Antiplaque ANPR:

§ 356.15 Antigingivitis/Antiplaque active ingredients. The active ingredient of the product consists of any of the following when used within the dosage limits and in the dosage form established for each ingredient:

. . . . .

(f) Zinc citrate 2% in a toothpaste alone and when combined in accordance with 356.26(p).

§ 356.26 Permitted combinations of active ingredients.

. . . . .

(s) The Antigingivitis/Antiplaque active ingredient identified in § 356.15(a) **and (f)** or the combination of ingredients identified in § 356.26(p) may be combined with any single Anticaries active ingredient identified in § 355.10 of this chapter and any single tooth desensitizer active ingredient identified in § 356.22.

Or more simply, the Antigingivitis/Antiplaque ANPR permits Zinc citrate 2% to be combined with Sodium monophosphate 1.14% and potassium nitrate 5% as proposed by the applicant.

B. STATEMENT OF GROUNDS

The proposed combination is safe, effective, and rational and thus suitable for OTC marketing for two reasons. First, an OTC toothpaste containing a combination of Sodium Monofluorophosphate 1.14%, Potassium Nitrate 5%, and Zinc Citrate 2% for the benefits of Anticaries, Hypersensitivity Pain Relief, and Antigingivitis/Antiplaque, respectively, meets FDA's criteria for a rational combination as discussed in Section b, below. Second, each of the proposed ingredients is safe and effective when used in toothpaste. As stated in the Anticaries Final Monograph and Oral Discomfort TFM, Fluoride and Potassium Nitrate are safe and effective for the Anticaries and Hypersensitivity Pain Relief, respectively. In the Antigingivitis/Antiplaque ANPR, Zinc Citrate was also determined to be safe for use as an Antigingivitis/Antiplaque active. However, given the evidence available, Zinc Citrate was considered Class III for efficacy at the time of the ANPR. Subsequent to the Antigingivitis/Antiplaque ANPR, Colgate has submitted studies it conducted establishing that Zinc Citrate is an efficacious Antigingivitis/Antiplaque agent, and is submitting one additional pivotal and supporting studies with this Petition.

1. The Proposed Product is a Rational Combination Under the Applicable Rulemakings

Colgate establishes below that the proposed product with a triple combination of active ingredients is a rational combination that should be permitted for OTC marketing, consistent with the position of the Subcommittee's recommendation .[2]

a. Background – Sodium Monofluorophosphate/Potassium Nitrate and Sodium Monofluorophosphate/Zinc Citrate Are Recognized Combinations

Sodium Monofluorophosphate is Category I for safety and efficacy as an Anticaries active ingredient under the Anticaries Monograph. (21 CFR § 355.10(b)(2)). Potassium Nitrate is Category I for safety and efficacy as a tooth desensitizer active ingredient under the Oral Discomfort TFM (56 Fed. Reg. 48,302). FDA has already recognized that Sodium Monofluorophosphate and Potassium Nitrate is a rational combination. FDA has, since 1992, permitted under its enforcement discretion the marketing of combination Anticaries/Antisensitivity combination products (57 Fed. Reg. 20,114, May 11, 1992-*Combination Drug Products Containing Potassium Nitrate and an Anticaries Ingredient; Marketing Status for Over-the-Counter Human Use; Notice of Enforcement Policy*).

In addition to the recognized safety and efficacy of the combination of Sodium Monofluorophosphate and and Potassium Nitrate, the evidence also supports the safety and efficacy of a Sodium Monofluorphosphate/Zinc Citrate combination for Anticaries and Antigingivitis/Antiplaque. Zinc Citrate was was considered to be Class III for efficacy at the time of the Antigingivitis/Antiplaque ANPR. Subsequent to the original call for data and in response to the Panel's recommendations, Colgate submitted two petitions to the Docket, each consisting of an additional well-controlled, 6-month plaque/gingivitis clinical study supporting the efficacy of a Sodium Monofluorophosphate/Zinc Cirate combination product for control of plaque and gingivitis. In addition, Colgate has marketed a Sodium Monofluorophosphate and Zinc Citrate toothpaste product (Viadent) in the US for over 20 years with safety comparable to typical toothpaste products. Moreover, as discussed below in this Petition, foreign marketing history supports the safety of the proposed triple combination.

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[2] The Independent Dental Plaque Subcommittee of the Nonprescription Drugs Advisory Committee of the Center for Drug Evaluation and Research ("Subcommittee") commenting in the Antigingivitis/Antiplaque ANPR.

b. FDA Has Data to Conclude that the Triple Combination is Rational

Colgate submits that the Agency should find the proposed triple active product to be a rational combination. This is supported by the Subcommittee's view articulated in the Antigingivitis/Antiplaque ANPR. It recommended that the following oral care combinations be considered rational: "(1) an antigingivitis/antiplaque active ingredient combined with an Anticaries active ingredient, (2) an Antigingivitis/ Antiplaque active ingredient combined with a tooth desensitizer active ingredient, and (3) an Antigingivitis/Antiplaque active ingredient combined with an Anticaries active ingredient and a tooth desensitizer active ingredient." (68 Fed. Reg. at 32,232). The Subcommittee further explained that "it is rational to combine oral health care ingredients that meet the regulatory requirements as well as the criteria adopted by the Subcommittee, together with suitable inactive ingredients, provided that the following six conditions are met:

a) each active ingredient makes a contribution to the claimed effect,

b) the active ingredients are safe and effective and combining the ingredients does not decrease the effectiveness of any individual ingredient,

c) combining the ingredients does not decrease the safety of the combination compared to a single ingredient,

d) the inactive ingredients are safe and do not interact with or otherwise inhibit the effectiveness of the active ingredients,

e) there is a significant target population that can benefit from the use of the combination, and

f) the combination contains adequate directions for use and is labeled with adequate warnings against unsafe use." (68 Fed. Reg. at 32,240)

FDA dissented from the Subcommittee's recommendations at that time, finding the data was insufficient to establish the safety and efficacy of a specific combination. (68 Fed. Reg at 32,232) Importantly, though, FDA also acknowledged that data could be submitted to establish the safety and efficacy of this rational combination. Accordingly, consistent with the Subcommittee's recommendation and FDA's request, Colgate submits supporting data demonstrating that its desired Sodium Monofluorophosphate, Potassium Nitrate, and Zinc Citrate combination product meets the six criteria for a rational combination. We explain below how the criteria are met.

Each of the three active ingredients in the desired combination makes a contribution to the claimed effect.

Sodium Monofluorophosphate 1.14% provides Anticaries protection. Under the Anticaries Final Monograph (21 CFR § 355), a Sodium Monofluorophosphate toothpaste at 1500 ppm fluoride ion (equivalent to 1.14% Sodium Monofluorophosphate) is Category I for both safety and efficacy for aiding in the prevention of dental cavities.

Potassium Nitrate 5% provides hypersensitivity pain relief. Potassium Nitrate is Category I for safety and efficacy as a tooth desensitizer active ingredient under the Oral Discomfort TFM (56 Fed. Reg. 48,302).

Zinc Citrate 2% provides antigingivitis/antiplaque efficacy. **Attachment 1** includes a table of all relevant clinical studies from previous submissions to the docket and additional studies in this Petition. Colgate is submitting one additional study with this Petition, **Attachment. 2**. This study by Mankodi/Nathoo compared the proposed combination (test) product to a commercially available 1500 ppm Fluoride (control) dentifrice. Plaque and gingival index scores for the intent to treat subjects were compared after six months. The test group was statistically significantly better than baseline ($p<0.05$) and the control group was not ($p>0.05$) with respect to plaque and gingival index scores. The test product was statistically significant in both plaque (20.6%) and gingival (18.9%) index scores.

All three ingredients in the desired combination are safe and effective and combining them does not decrease the effectiveness of any individual ingredient, nor does it decrease the safety of the combination compared to a single ingredient.

As summarized below, multiple studies demonstrate that the efficacy of each of the three ingredients in the desired combination product is not negatively impacted by the presence of each other.

As described in **Attachment 3**, an Enamel Fluoride Uptake/Enamel Solubility Reduction study was conducted under the Anticaries Final Monograph requirements to show the bioavailability of Fluoride for use as an Anticaries active ingredient in a Sodium Monofluorophosphate/Potassium Nitrate/Zinc Citrate toothpaste. This study demonstrates that, in the presence of the Potassium Nitrate and Zinc Citrate, the Sodium Monofluorophosphate retains the same level of bioavailability and is not negatively affected by the other two ingredients.

As described in **Attachment 4**, a double-blind stratified parallel *in vivo* study was conducted on Sodium Monofluorophosphate, Potassium Nitrate, and Zinc Citrate. This study demonstrates that the efficacy of Potassium Nitrate for hypersensitivity pain relief is not negatively impacted by the presence of Sodium Monofluorophosphate and Zinc Citrate. This study by Hu/Proskincompared the proposed combination (test) product to a commercially available 5% Potassium Nitrate and 0.306% Sodium Fluoride (control) dentifrice. Note the 2% Zinc Citrate contained in the test product was not identified as an active ingredient for purposes of this sensitivity study. At both the four-week and eight-week examination, no statistical differences were indicated between the test and control groups with respect to tactile sensitivity or air blast scores. Both were statistically significantly ($p<0.05$) compared to baseline at both time points.

Combining the ingredients in the desired combination does not decrease the safety of the combination compared to a single ingredient.

As discussed above, the safety of each ingredient for their respective benefits is established. In addition, the evidence supports their safety in a triple-combination product. Consistent with the safety data obtained during clinical studies conducted by Colgate in the United States, the foreign marketing history of the desired combination detailed in **Attachment 5** supports the safety of the proposed triple combination. With over 75 million tubes sold globally to date, including over 7 million in Europe (where the triple combination is exactly that proposed in this Petition including Potassium Nitrate), Colgate has not received or detected a single serious adverse event with its triple combination product. This marketing history demonstates that the safety of the combination with Potassium as Potassium Nitrate is well-established in all major European markets where it has been marketed since 2006. In addition, the same combination with Potassium as the Citrate salt has been marketed extensively in Asia, Latin America, Australia and New Zealand.

Global Product Distribution: For the time period since the proposed formulation was globally introduced in 2006 up to April 4, 2012, a total of 76,559,524 units of product have been distributed globally. Each unit contains approximately 4.0 oz of the proposed product formulation consisting of the three active ingredients – Zinc Citrate, Sodium Monofluorophosphate, and Potassium Nitrate. For business reasons, Potassium Citrate is used in place of Potassium Nitrate in certain regions, as noted. In most countries, potassium nitrate (5%), potassium chloride (3.75%) and potassium citrate (5.5%) are used interchangeably since all provide 2% potassium ion, which is the clinically proven

active moiety for sensitivity relief. The safety for all these salts is well established.[3]

Reported Adverse Event Data: For the time period since the proposed formulation was globally introduced in 2006 up to April 4, 2012, a total of 240 adverse events were reported (see **Attachment 6**). The adverse experiences reported for the formulation are considered to be non-serious. Applying the FDA definitions for adverse event reporting, in no case was there an adverse event that would be classified as a serious, unexpected event.

As expected, 213 of the 240 adverse events reported were associated with the oral cavity. The majority of the 213 oral cavity adverse reports were mouth irritation (85), tooth sensitivity (48), and canker sores (13).

The adverse event data reported for the formulation is consistent with other OTC dentifrice products. In addition, the directions for use for the proposed formulation are consistent with other OTC toothpastes claiming the same indications.

The inactive ingredients in the desired formulation are safe and do not interact with or otherwise inhibit the effectiveness of the active ingredients.

It has been well accepted by the scientific and regulatory bodies that the safety of finished products can be ensured on the basis of knowledge of the safety of the ingredients they contain.[4] The inactive ingredients in the proposed formula are commonly used oral care ingredients and have been determined to be safe by the FDA, other global regulatory agencies, and by Colgate ingredient analysis. See **Attachment 7.** Additionally, the foreign marketing data and clinical results included in this Petition establish there is no interaction that impacts safety.

There is a significant target population that can benefit from the use of the desired formulation.

The target population for the proposed combination toothpaste is consumers desiring an OTC oral care product that aids in the Anticaries and Antigingivitis/Antiplaque, while also treating Hypersensitivity Pain Relief. Given

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[3] American Journal of Denistry, Vol 23, Sp Is A, May 2010, Cummings, Diane.

[4] The Scientific Committee on Consumer Safety (SCCS) Notes of Guidance for Testing of Cosmetic Ingredients and Their Safety Evaluation, 7th Revision SCCS/1414/11 adopted 14 Dec 2010.

the high prevalence of each condition, there is a large target population that would benefit from all three indicated uses. Short of buying and using multiple oral care products, the target population would lack access to effective treatment or prevention for either sensitivity or gingivitis. The proposed combination thus provides a public health benefit for the target population. The prevalence of each condition is set forth below.

Anticaries prevention: In the United States, 92% of adults 20 to 64 have had dental caries in their permanent teeth.[5]

Hypersensitivity Pain Relief: Dentinal hypersensitivity presents as early as the teen years and through old age. There is a wide range in the reported prevalence of dentinal hypersensitivity, with publications citing prevalences of up to 98% depending on the population group. The highest prevalence is seen in periodontal patients, with a reported range of 60% - 98%.[6] In the general population, up to 30% of adults have dentinal hypersensitivity at some time,[7] although prevalences of up to 57% have been reported.[8]

Antigingivitis/Antiplaque: In the United States, 50.3% of the population aged 30 years and older and 52.9% age 20 years and older have gingivitis.[9]

The desired combination is labeled with adequate directions for use and warnings.

The proposed label would be in compliance with applicable general labeling regulations for OTC drugs (21 CFR Part 201) and the applicable rulemakings, namely the Anticaries Final Monograph, Oral Discomfort TFM, and Antigingivitis/Antiplaque ANPR. The directions for use, warnings and draft label are included in **Attachment 8**.

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[5] http://www.nidcr.nih.gov/DataStatistics/FindDataByTopic/DentalCaries/DentalCariesAdults20to64.htm (visited April 23, 2012).

[6] Catherine D. Saylor BSDH, MS and Pamela R. Overman BSDH, MS, EdD, Dentinal Hypersensitivity: A Review (Feb. 2011).

[7] Trushkowsky RD, Oquendo A., Treatment of dentin hypersensitivity, Dent Clin North Am., July 2011; 55(3):599-608.

[8] Catherine D. Saylor BSDH, MS and Pamela R. Overman BSDH, MS, EdD, Dentinal Hypersensitivity: A Review (Feb. 2011).

[9] Albandar JM and Kingman A, Gingival recession, gingival bleeding and dental calculus in adults 30 years of age and older in the United States, 1988-1994, J. Periodontol, 1999; 70:30-43.

c. Conclusion that the Combination is Rational

This Citizen Petition requests that the Agency allow the marketing of a Sodium Monofluorophosphate 1.14%, Potassium Nitrate 5%, and Zinc Citrate 2% product that provides to the public an innovation in oral care that clearly meets the requirements outlined in the applicable rulemakings for a combination of ingredients that are generally recognized as safe and effective for OTC use where each contributes to the claimed effects and where safety and efficacy are not compromised by the combination. This innovation also provides the public with the convenience of having the three benefits in a single product.

2. Interim Enforcement Policy

The Regulatory Action Guidance (Compliance Policy Guide Sec 450.300, OTC Drugs) allows for interim marketing (at risk) for combination products that meet outlined conditions. In this case, the review of Sodium Monophosphate is final and there is a proposed Category I status on safety and efficacy for for Postassium Nitrate. Zinc Citrate is recognized as safe in the Anticaries/Antiplaque TFM, and Colgate has reviewed and submitted data in this petition to establish its efficacy. This Petition also provides evidence that the safety and efficacy of each individual ingredient is preserved in the combination, Colgate the other, strengthening the case for interim marketing. With the submission of confirmatory data, Colgate believes the conditions are met for the desired combination, and interim marketing should be allowed at this time. Colgate requests that during the process to amend the applicable rulemaking, FDA issue a notice of enforcement policy permitting the interim marketing of the combination before a Final Amendment is published, as it did with Potassium Nitrate and Fluoride in 1992 (57 Fed. Reg. 20,114).

C. ENVIRONMENTAL IMPACT

This petition qualifies for a categorical exemption from the requirements of submission of an environmental assessment (21 CFR § 25.31(c)).

D. ECONOMIC IMPACT

FDA specifies in 21 CFR § 10.30(b) that specific economic information is to be provided only when requested by the Commissioner following the review of the petition.

E. CERTIFICATION

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

In support of Commissioner's stated goal of FDA facilitating innovation, Colgate respectfully requests that this petition be granted.

Respectfully,

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2012 MAY -7 P 2:52

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Phone:	301-827-6881	**Date:**	May 7, 2012
Re:	Citizen Petition	**cc:**	

■ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

• **Comments:** Ms., Ortega:

As we discussed, the confidentiality statement (page 12) was included in our petition in error. Please remove both page 12 and 13, and replace with this updated page 12 (identical to the original page 13).

Thank you for your time and effort.

Regards,

Charles Ireland