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Dockets Management Branch
Room 123 (HFA-305)
Food and Drug Administration
Department of Health and Human Services
12420 Parklawn Drive
Rockville, Maryland 20857

CITIZEN PETITION

Pursuant to 21 C.F.R. §10.30, the undersigned, attorneys for N2 Products Corporation, 2 Learning Lane, Levittown, Pennsylvania 19054, hereby submit this petition under Sections 505, 513 and 515 of the Federal Food, Drug, and Cosmetic Act ("the Act"), requesting the Commissioner of Food and Drugs ("the Commissioner") to issue an order obligating manufacturers and distributors of all commercially sold root canal filling materials and sealers to fulfill the new drug approval or medical device premarket approval requirements of the Act, and to take related additional action.

A. Action Requested

This petition requests the Commissioner to issue the following order:

1. That any root canal filling material or sealer containing a chemical ingredient that produces disinfecting or other drug activity is a new drug requiring Food and Drug Administration ("FDA") approval of a

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new drug application ("NDA") to be lawfully distributed for sale in interstate commerce.

2. That any other root canal filling material or sealer is a Class III medical device requiring FDA approval of a premarket approval application ("PMA") to be lawfully distributed for sale in interstate commerce, and that any such product presently classified as a Class I or Class II medical device be reclassified as a Class III medical device.

This petition further requests the following:

3. That the FDA send warning letters to the manufacturers and distributors of the root canal filling materials and sealers named in this petition, directing them to cease commercial distribution thereof pending NDA or PMA approval.

4. That the FDA undertake an investigation to determine all other manufacturers and distributors of root canal filling materials and sealers in the United States, and send them the same kind of warning letters described in paragraph 3 above.

B. Statement of Grounds

In 1975, the FDA took the position that root canal filling materials and sealers containing paraformaldehyde are new drugs requiring approval of NDA's be-

fore they can be commercially distributed in interstate commerce.* The agency based this position on the ground that paraformaldehyde, when included as a disinfectant ingredient in such materials or sealers, is not generally recognized as safe and effective for such use. Id.

The petitioner, N2 Products Corporation, has complied with this request by filing an NDA for N2 Universal, a root canal filling material and sealer containing paraformaldehyde as a disinfecting agent. This NDA is currently in the late stages of review by the FDA's Center for Drug Evaluation and Research.

However, there are numerous other root canal filling materials and sealers that are commercially distributed in the United States, none of which has ever been subjected to premarket clearance by the FDA. Some of these materials contain disinfecting ingredients; others contain other drug ingredients; all of them contain ingredients which have been shown to be toxic; and none of them are generally recognized among qualified

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* Statement of J. Richard Crout, M.D., Director, Bureau of Drugs, Food and Drug Administration, Hearings Before a Subcommittee on Intergovernmental Relations and Human Resources, Committee on Government Operations, U.S. House of Representatives, 94th Cong., 1st Sess., Oct. 31, 1975, at 71-74 (see attached Exhibit 1).

experts as safe and effective for their intended use. Therefore, FDA preclearance requirements should apply to all such products, to assure even-handed treatment of similarly-situated FDA regulated products and adequate protection of the public health.

1. Root Canal Filling Materials and Sealers: Background

Endodontic (root canal) therapy is a dental procedure that requires removal of pulp tissue from the canal of a decayed or damaged tooth to the depth of the tooth's root apex, and the subsequent filling and sealing of the canal. Such treatment preserves the treated tooth from extraction, and is one of the most widely used dental restorative treatments in the United States.

In root canal treatment, the pulp is extirpated (removed) from the canal by hand-held or mechanized instruments, and the space in the canal previously occupied by the pulp is then obturated (filled), and sealed to prevent infection. The most commonly used filling materials, which fill the extirpated canal cavity, are core materials such as gutta percha and silver cones. The most commonly used sealers, which provide a tight seal of the obturated canal to prevent ingress and growth of bacteria, are zinc oxide-eugenol based sealers, resin-based sealers, sealers to which disinfectant or anti-

inflammatory agents are added, and sealers containing calcium hydroxide to provide a long-lasting antibacterial effect. Sealers are used alone or in combination with core filling materials.

2. The Toxicity and Lack of Demonstrated Effectiveness of Root Canal Filling Materials and Sealers

All root canal filling materials and sealers have been shown to be cytotoxic.* Their components may be found in vital tissue and in several organs.** Most filling materials and sealers produce an initial inflammatory reaction in connective tissues, followed by a chronic foreign body reaction.*** As the materials disintegrate in tissue fluids, macrophages are activated and

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* Harty, F.J., Endodontics in Clinical Practice, Wright, 3d Ed. 1990 at 192-197 (see attached Exhibit 2). See also, Orstavik, D. and Mjor, I.A. Histopathology and X-ray microanalysis of the subcutaneous tissue response to endodontic sealers. J. Endodont., 14, 13 (1988).

** Harty, Endodontics in Clinical Practice, at 192. See also Feiglin B. and Reade, P.C. The distribution of (^{14}C) leucine and ^{85}Sr labeled microspheres from rat incisor root canals. Oral Surg. Oral Med. Oral Path., 47, 277 (1979); Orstavik, D. Weight loss of endodontic sealers, cements and pastes in water. Scand. J. Dent. Res., 91, 316 (1983b); Tronstad, L., Barnett, F. and Flax, M. Solubility biocompatibility of calcium hydroxide-containing root canal sealers. Endod. and Dent. Traumatol., 4, 152 (1988).

*** Seltzer, S., Endodontology, Lea & Febiger, 2d Ed. 1988 at 292 (see attached Exhibit 3).

elaborate enzymes, such as collagenase, which cause tissue destruction. Id. The presence of these foreign materials in periapical tissues (tissues surrounding the base of the root canal apex) causes persistence of tissue breakdown. Id.

The petitioner has submitted a substantial body of data in its NDA demonstrating the safety of its particular root canal filling material and sealer containing paraformaldehyde as a disinfectant, in endodontic treatment. No other root canal filling material or sealer has been demonstrated to be safe for this use by this quantum or quality of data.

There is also a variability among root canal filling materials and sealers in contributing to the desired clinical effects of sealing the canal without infection and permitting retention of the endodontically-treated tooth.* In its NDA, the petitioner has submitted substantial evidence of the effectiveness of its particular root canal filling material and sealer, containing paraformaldehyde as a disinfectant, in endodontic therapy. There are no reported adequate and well-controlled

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* See Grossman, L., Endodontic Practice, Lea & Febiger, 11th Ed. 1988 at 266-268 (see attached Exhibit 4).

clinical studies establishing such effectiveness of any other root canal filling material or sealer.

3. FDA Preclearance Requirements Must Be Applied to All Root Canal Filling Materials and Sealers

By virtue of the lack of safety and effectiveness studies that are required in an NDA, there is a lack of general recognition that root canal filling materials and sealers are safe, and a lack of general recognition that they are effective, in endodontic therapy. See Weinberger v. Hynson, Westcott & Dunning, Inc., 412 U.S. 609 (1973). Therefore, each such material containing a disinfecting or other therapeutic agent is a new drug requiring an approved NDA. Id.; 21 U.S.C. §§321(g),(p) and 505; Statement of J. Richard Crout, M.D., supra, at 72 (see Exhibit 1). Similarly, each such material without a drug ingredient is a Class III medical device for which a PMA is required to provide reasonable assurance of its safety and effectiveness. 21 U.S.C. §§321(h), 360c(a)(1)(C), and 360e.

The petitioner has fulfilled these requirements by its NDA submission. However, numerous root canal filling materials and sealers have been commercially distributed and sold to dentists for many years without this requisite FDA preclearance. This petition requests

the Commissioner to enforce the law against these materials. The FDA is required, by the Act and the due process clause of the Fifth Amendment to the United States Constitution, to apply evenhanded regulatory standards to similarly-situated regulated products. United States v. Diapulse Corporation of America, 748 F.2d 56 (2d Cir. 1984); United States v. Undetermined Quantities of an Article of Drug ... "Exachol", 716 F.Supp. 787 (S.D.N.Y. 1989).

Manifestly, protection of the public health also demands that these unapproved filling materials and sealers be subjected to appropriate FDA preclearance standards.

4. Particular Filling Materials and Sealers: Paraformaldehyde-and Formaldehyde-Containing Products

The following are commercially marketed root canal filling materials and sealers that contain paraformaldehyde or formaldehyde:

(i) White One-Step Formula, manufactured by the Dental Clearing House of Simsbury, Connecticut (see advertisements in attached Exhibit 5). This is a paraformaldehyde-containing root canal sealer similar to the petitioner's product, which has falsely been advertised that it is "FDA-approved" and

can be lawfully purchased commercially in bulk (see Exhibit 5).

(ii) Brut Drug's Endodontic Formula, manufactured by Brut Drug Company, Inc., P.O. Box 566, Keansburg, New Jersey 07734 (see advertisement, price list and order form in attached Exhibit 6). This is also a para-formaldehyde-containing root canal sealer similar to the petitioner's product, which has been falsely advertised as available in 60 gm. bulk bottles without a prescription, and falsely represented as "registered with the Food and Drug Administration" (see Exhibit 6).

(iii) AH26, manufactured by DeTrey Dentsply of Zurich, Switzerland, and distributed in the U.S. by ASH-USA, Inc., P.O. Box 872, York, Pennsylvania 17405 (see labeling in attached Exhibit 7). AH26 is an epoxy resin-based sealer that releases formaldehyde during its setting action.* It causes a severe

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* Formaldehyde is a liquid form of paraformaldehyde.

inflammatory reaction that can last up to 30-60 days.* It is also a potent allergen. Id. These products should be made to adhere to the same NDA approval requirement as all paraformaldehyde-containing root canal filling materials.

5. Particular Filling Materials and Sealers Containing Other Drug Ingredients

(a) The following are commercially distributed root canal filling materials and sealers containing the drug ingredient calcium hydroxide:

(i) Calciobiotic Root Canal Sealer (CRCS), distributed by The Hygenic Corporation, 1245 Home Avenue, Akron, Ohio 44310 (see labeling in attached Exhibit 9);

(ii) Sealapex, distributed by Kerr Manufacturing Company, 28200 Wick Road, Romulus, Michigan 48174; and

(iii) TempCanal, distributed by Pulpdent Corporation, 80 Oakland Street, Watertown, Massachusetts 02272 (see labeling in attached Exhibit 10).

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* Tronstad, L., Clinical Endodontics, Thieme, 1st Ed. 1991 at 162-163 (see attached Exhibit 8).

The drug ingredient calcium hydroxide is used in these sealers to provide a broad, long-lasting antibacterial effect. However, the pH of CRCS is less than the 12.9 required to produce such an effect, and there is no evidence of this or any therapeutic effect for Sealapex.* Calciobiotic, Sealapex and TempCanal should all be required to satisfy the requirement of NDA approval.

(b) ESPE Ketac-Endo, distributed by ESPE-Premier Sales Co., P.O. Box 111, Norristown, Pennsylvania 19404, is a glass ionomer root canal sealer. The product "penetrates and seals dentinal tubules," and "has been shown to release flouride ions of a long period of time, resulting in antibacterial properties" (emphasis added) (see labeling in attached Exhibit 12). This newly marketed product contains drug ingredients and makes drug labeling claims. It should therefore be required to fulfill NDA approval requirements.

6. Particular Filling Materials and Sealers That Should be Regulated as Class III Medical Devices

The following are commercially marketed root canal filling materials and sealers that, while not con-

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* Tronstad, Clinical Endodontics, at 104, 165 (see attached Exhibit 11).

taining drug ingredients, have produced toxic effects mandating that they be regulated as Class III medical devices requiring PMA approval:

(i) Diaket, manufactured by ESPE of Seefeld, Germany and distributed in the United States by ESPE-Premier Sales Corp., 1710 Romano Drive, Norristown, Pennsylvania 19404. Diaket is a polyvinyl resin-based sealer which has marked toxic and irritating effects, including severe initial inflammatory reactions.*

(ii) Hydron, manufactured and distributed by NPD Dental Systems of Melville, New York. Hydron is a hydrophylic gel sealer that has produced persisting inflammation and questionable efficacy results.**

(iii) Zinc oxide-eugenol-based sealers. These include Grossman's Cement and Procosol, distributed by Star Dental of Coshohocken, Pennsylvania; Tubli-Seal and Kerr Pulp

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* Tronstad, Clinical Endodontics, at 162 (see Exhibit 7); Harty, Endodontics in Clinical Practice, at 194 (see Exhibit 2).

** Harty, Endodontics in Clinical Practice, at 194 (see Exhibit 2).

Canal Sealer, both distributed by Kerr Manufacturing Company, 28200 Wick Road, Romulus, Michigan 48174 (see labeling in attached Exhibit 13); Roth Root Canal Cement, distributed by Roth International Ltd., 669 West Ohio Street, Chicago, Illinois 60610 (see labeling in attached Exhibit 14); Endomet, distributed by Septodont, Inc., 245 C Quigley Blvd., New Castle, Delaware 19720 (see labeling in attached Exhibit 15); and Nogenol, distributed by Coe Laboratories, division of GC America, Inc., 3737 West 127th Street, Chicago, Illinois 60658.

Practically all zinc oxide-eugenol based sealers, including the above formulations, are cytotoxic, and this response may be long-lasting compared to other sealers.* A noted hazard in the use of eugenol-containing sealers is the potential for sensitization. Id.

(iv) Gutta percha-solvent sealers. These formulas consist of combinations of

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* Harty, Endodontics in Clinical Practice, at 193 (see Exhibit 2).

gutta percha (a material made from coagulated sap of certain tropical trees) and an organic solvent. Kloropercha (Chloropercha) is a combination of gutta percha and chloroform. Eucapercha is a combination of gutta percha and eucalyptol. While gutta percha alone has been classified as a Class I device when used as an endodontic filling material (21 C.F.R. §872.3850), these combinations require regulation as Class III devices because chloroform and eucalyptol are cytotoxic.*

7. Other Materials

The materials identified in sections B(4), (5) and (6) of this petition are root canal filling materials and sealers about which the petitioner has the most knowledge. There are other formulations on the market which should also be investigated and made the object of regulatory letters requiring them to adhere to NDA or PMA requirements. Among these are: Wachs Root Canal Sealer, distributed by Young Dental Manufacturing Co., 13705

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* Harty, Endodontics in Clinical Practice, at 194-95 (see Exhibit 2). It should be noted that resin-based endodontic filling materials have been classified as Class III devices when combined with chloroform (see 21 C.F.R. §872.3820).

Shoreline Court East, Earth City, Missouri 63045; Endo-Seal Cement, distributed by Centrix, Inc., 30 Stran Road, Milford, Connecticut 06460 (see labeling in attached Exhibit 16); and U/P Root Canal Cement, distributed by Sultan Chemists, Inc., 85 West Forest Avenue, Englewood, New Jersey 07631.

C. Environmental Impact

Preparation of an environmental assessment is not required, since the requested action is a recommendation for an enforcement action. See 21 C.F.R. §25.2(a)(2).

D. Economic Impact

To be supplied if requested by the Commissioner.

E. Certification

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

Respectfully submitted,

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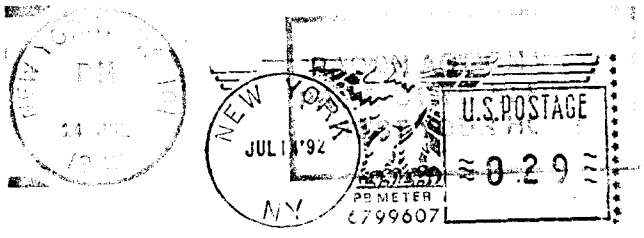

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