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February 26, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Attention: Docket No. 2003D-0391

Re: Docket No. 2003D-0391: Draft Guidance for Industry and FDA Staff; Class II Special Controls Guidance Document: Dental Precious Metal Alloys and Class II Special Controls Guidance Document: Dental Base Metal Alloys; Availability: 68 Fed. Reg. 67196 (December 1, 2003)

Dear Sir or Madam:

I am enclosing for filing in the above referenced matter the Comments of the Nickel Institute. If you have any questions regarding the Comments, please contact me or Mr. Bruce A. McKean, Director of Environmental Affairs for the Nickel Institute, at the mailing address, e-mail address, or telephone number shown on the cover page of the Comments.

Very truly yours,

Neil J. King

Neil J. King

Enclosure

20030-0391 C1

BEFORE THE
DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

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| Dental Devices; Gold Based Alloys, Precious Metal Alloys, and Base Metal Alloys; Designation of Special Controls Proposed Rule: 68 Fed. Reg. 67097 (December 1, 2003) | Docket No. 2003N-0390 |

and

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| Draft Guidance for Industry and FDA Staff; Class II Special Controls Guidance Document: Dental Precious Metal Alloys and Class II Special Controls Guidance Document: Dental Base Metal Alloys; Availability: 68 Fed. Reg. 67196 (December 1, 2003) | Docket No. 2003D-0391 |

COMMENTS OF

THE NICKEL INSTITUTE

Communications Regarding These Comments Should Be Directed to:

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February 26, 2004

The Nickel Institute ("Ni-I") is pleased to submit these Comments on the Food and Drug Administration's ("FDA") proposal to amend the classification of dental base metal alloy devices under the Federal Food, Drug, and Cosmetic Act ("FFDCA"). The proposal also would designate a special control for these devices and exempt them from premarket notification requirements when the special control has been adhered to. 68 Fed. Reg. 67097 (December 1, 2003). The special control for these devices would be FDA's "Class II Special Controls Guidance Document: Dental Base Metal Alloys," a draft of which ("Draft Guidance") was released for public comment simultaneously with the proposed rule. 68 Fed. Reg. 67196 (December 1, 2003). Once the proposed rule has been finalized, a firm claiming exemption from premarket notification requirements would "need only show that its device meets the recommendations of the [Dental Base Metal Alloys Guidance] or in some other way provides equivalent assurances of safety and effectiveness." 68 Fed. Reg. at 67098.

The Nickel Institute, an association of the western world's principal nickel producers, supports this proposal. However, as discussed below, Ni-I believes a clarification should be made regarding the scope of the Guidance, and a change should be made in the Labeling section of the Draft Guidance.

Section 1 of the Draft Guidance ("Scope") says that "[a] base metal alloy may be primarily composed of chromium, cobalt, and nickel, with lesser amounts of other elements such as molybdenum and aluminum."[1/] This statement could be construed to imply that a stainless steel dental alloy (which consists primarily of iron with lesser and varying amounts of chromium and nickel) or a shape-memory alloy like nitinol

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1/ Draft Guidance at 2.

(consisting of 50% nickel and 50% titanium) is not considered a "base metal alloy" for these purposes. If that is FDA's intent, it should make the point clear and explain why. If, as we assume, that is not FDA's intent, it should clarify that the term "base metal alloy" encompasses a broader range of materials than the current language of the Draft Guidance implies.

Section 6 of the Draft Guidance recommends that the manufacturer insure the biocompatibility of a dental device by complying with the requirements of standard ISO-10993 for a permanent contact, external communicating device on tissue, bone, or dentin.[2] Among the tests required by ISO-10993 for a permanent contact, external communicating device on tissue, bone, or dentin is the test for sensitization (ISO-10993-10).[3] We agree with this recommendation. However, assuming the device performs satisfactorily when subjected to the sensitization test of ISO-10993-10, we see no reason why Section 7 of the Draft Guidance recommends that labeling for the device "include a contraindication for nickel hypersensitive individuals, if the alloy composition contains >1% Ni."[4]

If a dental alloy purposefully contains nickel at all, it is highly likely that the nickel content will exceed 1 percent. Consequently, this labeling recommendation could have a severe negative impact on the use of nickel alloys in dental applications, despite the many useful properties that nickel contributes to dental alloys and the long history of its

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[2] *See id.* at 4.

[3] *See* ISO-10993-1, Table 1.

[4] Draft Guidance at 5.

use for these purposes. Such an outcome is neither justified nor in the best interests of patients.

The nickel content of an alloy does not determine its potential ability to sensitize an individual or to elicit a sensitization reaction. That will depend instead on the rate of release of nickel ions (through corrosion or abrasion) under the conditions of use. The European Union has recognized this point in what is colloquially referred to as the "Nickel Directive."[5/] While the EU Nickel Directive is concerned with potential allergic contact dermatitis associated with dermal exposure, the focus on release of nickel ions (as opposed to a material's nickel content) is equally appropriate in the intra-oral environment. Indeed, the oral mucosa appear to be far more resistant to allergic reactions than the skin. At the same time, corrosion and abrasion rates of intra-oral appliances tend to be low during service, thereby limiting the release of nickel ions. Furthermore, in the intra-oral environment, the rate of ion release from a dental alloy device generally will diminish over time.

For these reasons, one would not expect the use of nickel-containing alloys in dental devices to present sensitization-related problems. And, despite a long history of use, there is no significant evidence of systemic disease or adverse patient reactions to dental alloys with a high nickel content. Similarly, in a study of ten nickel-sensitive

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[5/] Council Directive 94/27/EC provides that objects (such as necklaces, earrings, bracelets, and the like) that come into direct and prolonged contact with the skin may not release more than 0.5 $\mu$g Ni/cm$^2$/week when tested in an artificial sweat solution. Currently, the Directive precludes the use of materials containing more than 0.05% nickel during epithelialization of the wound caused by piercing the ears. However, a technical review committee has recommended that this latter provision be changed to a release-based standard in recognition of the fact that nickel release, not nickel content, is the relevant factor in causing sensitization or eliciting sensitization reactions. This recommendation is expected to be adopted when the Directive comes up for review.

individuals with fixed dental prostheses containing 66% nickel, no adverse reactions were detected in follow-up examinations over a period of 12 to 40 months.[6] These points and related issues are discussed at length in a publication entitled "The Safety of Nickel in Dental Alloys," a copy of which is attached to these Comments as Appendix 1.

In sum, as long as the alloy has performed satisfactorily when tested for sensitization in accordance with ISO-10993-10, there is no reason to warn against use of the alloy in "nickel hypersensitive individuals" (a term that undoubtedly means different things to different people), just because the alloy contains more than 1 percent nickel. Such a warning is both unjustified as a matter of science and contrary to the best interests of patients. The labeling recommendation in Section 7 of the Draft Guidance should, therefore, be removed.

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[6] *See* Spiechowicz, E., *et al.* (1984). Oral exposure to a nickel-containing dental alloy of persons with hypersensitive skin reactions to nickel. Contact Dermatitis. 10(4):449-50; Spiechowicz, E., *et al.* (1999). A long-term follow-up of allergy to nickel among fixed prostheses wearers. Eur. J. Prosthodont. Rest. Dent. 7(2/3):41-44.