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Gerald Austin  
c/o Eva Kasparova  
Sezimova 9  
14000 Prague 4  
CZECH REPUBLIC

Re: Docket No. 2004P-0411/CP1

Dear Mr. Austin:

This letter responds to your citizen petition dated September 8, 2004. You request that the Food and Drug Administration (FDA) act immediately to compel the enforcement and regulation of amyl nitrite inhalant pursuant to FDA's regulation at 21 CFR 250.100 as it relates to specific Internet Web sites.

FDA has considered the information submitted in your petition, as well as comments submitted to the docket, including comments from the Committee to Monitor Poppers, and other information. We address your request in this response. For the reasons explained below, your petition is denied.

## I. BACKGROUND

### A. Amyl Nitrite

Amyl nitrite is a vasodilator that was originally approved as a prescription drug product for treatment of angina pectoris (angina). Amyl nitrite is a member of the family of volatile alkyl nitrites that also includes isobutyl (butyl) nitrite and isopropyl nitrite. Alkyl nitrites act primarily to dilate blood vessels and relax smooth muscle.

Alkyl nitrites are commonly abused inhalants in the United States.<sup>1</sup> Abuse among segments of the homosexual male population has been reported for several decades.<sup>2</sup> Among homosexual

<sup>1</sup> Haverkos, H.W., and D.P. Drotman, "National Institute of Drug Abuse (NIDA) Technical Review: Nitrite Inhalants," *Biomedicine & Pharmacotherapy*, 50:228-230, 1996.

<sup>2</sup> Haverkos, H.W., A. Kopstein, H. Wilson, and P. Drotman, "Nitrite Inhalants: History, Epidemiology, and Possible Links to AIDS," *Environmental Health Perspectives*, 102:858-861 at 859, 1994. There is some evidence of abuse among teenagers and young adults as well, see NIDA, *Monitoring the Future: National Survey Results on Drug Use, 1975-1992, Volume I: Secondary School Students*, NIH Pub. No. 93-3597, 1993, and NIDA *Monitoring the Future: National Survey Results on Drug Use, 1975-2003, Volume I, Secondary School Students*, NIH Pub. No. 04-5507, 2003, at table 14, page 173.

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men, alkyl nitrites are used as an adjunct to sexual behavior and are perceived as enhancing sexual function and pleasure.<sup>3</sup> These products are referred to colloquially as "poppers."<sup>4</sup> Alkyl nitrite products intended for abuse frequently are marketed for diverse uses, including as videohead cleaners or room odorizers. Products intended for abuse often are sold over the Internet on Web sites targeting homosexual men.<sup>5</sup>

## B. Regulatory History

Amyl nitrite was initially marketed as a prescription drug for treatment of angina in the United States in 1937 and remained a prescription drug until 1960, when FDA eliminated the prescription requirement. In the 1960s, other drug products began to replace amyl nitrite as the preferred treatment for angina. In the late 1960s, pharmacists and drug manufacturers noticed widespread purchases of over-the-counter (OTC) amyl nitrite by apparently healthy young men. These OTC purchases became the impetus for the FDA to reinstate the prescription requirement in 1969.<sup>6</sup>

While amyl nitrite inhalant remains available by prescription,<sup>7</sup> an underground market has emerged that allows for continued abuse. As explained above, in an attempt to avoid enforcement actions under the Federal Food, Drug, and Cosmetic Act (the Act), manufacturers may promote their products for allegedly diverse uses such as room odorizers or videohead cleaners, although these promotions are directed to homosexual men.

FDA has jurisdiction over drugs, as defined in section 201(g) of the Act (21 U.S.C. 321(g)). FDA's regulations state that amyl nitrite inhalant is restricted to sale on the prescription of a licensed practitioner, and is misbranded unless its labeling bears adequate information for the drug's safe and effective use by physicians and its label bears the statement "Rx only"

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<sup>3</sup> The acute effects of nitrite inhalants include relaxation of smooth muscle causing intense peripheral vasodilation, flushing, a fall in blood pressure and a reflex increase in heart rate to maintain perfusion of vital organs. Vasodilation of cerebral vessels causes an increase in intracranial pressure. Headache, nausea, and fainting are common consequences of nitrite inhalation. Nitrite inhalants may produce skin and tracheo-bronchial irritation and may trigger an allergic reaction. Alkyl nitrites are flammable and explosive. See H. Haverkos, J. Dougherty (editors), NIDA Research Monograph 83: *Health Hazards of Nitrite Inhalants*, 1988, at pp 28-38.

<sup>4</sup> The original packaging of these drug products was glass ampoules enclosed in mesh. When crushed between the fingers, they made a popping sound, thus the nickname "poppers" evolved.

<sup>5</sup> These products also may be sold in other venues, including adult bookstores, sex clubs, and bars.

<sup>6</sup> Haverkos, H.W., A. Kopstein, H. Wilson, and P. Drotman, "Nitrite Inhalants: History, Epidemiology, and Possible Links to AIDS," *Environmental Health Perspectives*, 102:858-861 at 858, 1994.

<sup>7</sup> The clinical indication in the package insert is for angina, although other products have become the preferred treatments for this use. Amyl nitrite is also used off-label to treat cyanide poisoning.

(21 CFR 250.100). FDA can initiate enforcement proceedings against violations of the Act, including interstate shipment of misbranded drugs. FDA has wide latitude in matters of enforcement discretion, and may choose not to take enforcement action under certain circumstances. (See, e.g., *Heckler v. Chaney*, 470 U.S. 821 (1985); *Schering v. Heckler*, 779 F.2d 683 (D.C. Cir. 1985).)

In 1988, Congress enacted a ban on the manufacture and retail sale of butyl nitrite (n-butyl nitrite, isobutyl nitrite, secondary butyl nitrite, tertiary butyl nitrite, and mixtures containing those chemicals).<sup>8</sup> The Consumer Product Safety Commission (CPSC) was given legal jurisdiction to enforce the ban. Manufacturers with illegal intent then began to market other alkyl nitrites, such as isopropyl nitrite, as "new and improved" room odorizers or videohead cleaners.<sup>9</sup> In 1990, Congress banned the manufacture and sale of all alkyl nitrites again giving CPSC legal jurisdiction to enforce these laws.<sup>10</sup> Butyl nitrite, isopropyl nitrite, and volatile alkyl nitrites are banned hazardous products under the Consumer Product Safety Act (CPSA). These bans are contained in section 8 of the CPSA (15 U.S.C. 2057a and 2057b). CPSC has taken action against distributors and manufacturers of volatile alkyl nitrites.<sup>11</sup>

## II. DISCUSSION

Your petition requests that FDA act immediately to compel the enforcement and regulation of amyl nitrite inhalant pursuant to 21 CFR 250.100 as it relates to the Web sites [www.vhcleaner.com](http://www.vhcleaner.com), <http://getbooked.com>, [www.poppersexpress.com](http://www.poppersexpress.com), and [www.nitroaroma.com](http://www.nitroaroma.com).<sup>12</sup>

The use of traditional enforcement actions against companies that market prescription drug products without a required prescription on Internet Web sites poses significant challenges. The

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<sup>8</sup> Anti-Drug Abuse Act of 1988 (Public Law 100-690, section 2404). The law includes an exception for commercial purposes. The term *commercial purpose* is defined to mean any commercial purpose other than for the production of consumer products containing volatile alkyl nitrites that may be used for inhaling or otherwise introducing volatile alkyl nitrites into the human body for euphoric or physical effects (15 U.S.C. 2057a(c)(2)).

<sup>9</sup> "Nitrate Inhalants: History, Epidemiology, and Possible Links to AIDS" at 858. Both FDA and CPSC are aware that cyclohexyl nitrites have been developed by manufacturers with illegal intent in another attempt to circumvent the law.

<sup>10</sup> Omnibus Crime Bill (Public Law 101-647, section 3202). This law also contains an exception for commercial purposes (15 U.S.C. 2057b(c)).

<sup>11</sup> See CPSC's Web site at [www.cpsc.gov](http://www.cpsc.gov).

<sup>12</sup> In a letter submitted to the docket on January 31, 2005, you state that the Web site [www.vhcleaner.com](http://www.vhcleaner.com) sells isobutyl nitrite in contravention of the Consumer Product Safety Act and the Federal Hazardous Substances Act and you suggest joint prosecution by the FDA and the CPSC. As stated above, CPSC, not FDA, has jurisdiction to enforce those statutes (15 U.S.C. 2057a).

broad reach of the Internet, its relative anonymity, and the ease of creating new or removing old Web sites, pose new challenges for the enforcement of the Act. Internet technology can obscure the source of the product and make it difficult to determine who is responsible for selling and shipping the product. FDA has found that many Internet sites are actually comprised of multiple related sites and links, and the parties to a transaction can be dispersed geographically and need never meet. All of these features pose substantial and novel impediments to enforcement.

The Web sites described in your petition that market the drug product amyl nitrite inhalant as a videohead cleaner or room odorizer are similar to many other Web sites marketing these products. Identification of those responsible for these Web sites, some of which are based outside the United States, is often difficult and resource intensive. FDA does not have the resources to bring enforcement actions against all of these Web sites, but just as important, those who market these products, when threatened with enforcement action, may shut down their Web sites and open new ones with relative ease, making enforcement efforts unproductive. While traditional enforcement actions remain an option, FDA does not view such action as the most productive use of limited Agency resources for deterring illegal sales of poppers.

FDA recognizes that the abuse of amyl nitrite inhalant and other poppers is a serious health issue, particularly for the segment of the homosexual male population that continues to use them.<sup>13</sup> There are reports in the literature that associate the use of nitrite inhalants with immunosuppression, increased risk of HIV transmission, and Kaposi's sarcoma.<sup>14</sup>

The approved labeling of the erectile dysfunction (ED) drug products Viagra, Cialis, and Levitra contains specific, although not identical, warnings against their concomitant use with poppers. These warnings were added after reports of deaths, cardiovascular events, and other adverse events were reported to FDA when ED drug products were combined with poppers.

Because of the special challenges presented by Internet sales of poppers and the Agency's limited resources, FDA is exploring other strategies to counter illegal Internet sale of poppers (including amyl nitrite inhalant) and to reduce the demand for these products. These efforts could include public outreach and consumer education. In addition, we may coordinate our efforts with CPSC to develop a consistent and effective approach to address the unlawful sale and abuse of poppers.

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<sup>13</sup> We note that the Committee to Monitor Poppers submitted to the docket more than 100 references that discuss research on the health effects and risks of popper use. These references are available in the public docket for this citizen petition.

<sup>14</sup> See "Nitrite Inhalants: History, Epidemiology, and Possible Links to AIDS"; NIDA Research Monograph 83: *Health Hazards of Nitrite Inhalants*.

### III. CONCLUSION

FDA concludes that the most effective use of Agency resources to target illegal Internet sales of amyl nitrite inhalant will be through public outreach and educational efforts designed to inform the public of the health effects and risks of popper use. This decision does not preclude further Agency action, either alone or in conjunction with CPSC or other Federal agencies with jurisdiction, against Internet Web sites engaged in the illegal sale of amyl nitrite inhalant and/or poppers.

For the reasons discussed above, your request that FDA take enforcement action against specific Internet Web sites engaged in the sale of amyl nitrite inhalant is denied.

Sincerely,

A handwritten signature in black ink, appearing to read "Galson", written over a horizontal line.

Steven K. Galson, M.D., M.P.H.

Director

Center for Drug Evaluation and Research