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BY HAND DELIVERY

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061 (HFA-305)
Rockville, Maryland 20852

RE: Require Certain Appearance Changes to Over-the-Counter Transdermal Nicotine Patches

Dear Sir or Madam:

CITIZEN PETITION

The undersigned, on behalf of a client, submits this Citizen Petition under Section 505 of the Federal Food, Drug, and Cosmetic Act ("FDC Act") and in accordance with the Food and Drug Administration's ("FDA's" or the "Agency's") regulations set forth at 21 C.F.R. §§ 10.25 and 10.30 to request that the Commissioner of Food and Drugs take certain actions with respect to Over-the-Counter ("OTC") Transdermal Nicotine Patches ("TNPs") to help avoid accidental pediatric exposures to nicotine.

I. ACTION REQUESTED

Petitioner requests that FDA require the sponsors of all marketing applications – whether approved under a New Drug Application ("NDA") pursuant to FDC Act § 505(b), or under an Abbreviated New Drug Application ("ANDA") pursuant to FDC Act § 505(j) – to include permanent, smudge-resistant product identifying labeling on the backing membrane of their OTC TNP drug products to help avoid accidental pediatric exposures to nicotine.

II. STATEMENT OF GROUNDS

A. Factual Background

TNPs are a type of nicotine replacement therapy that have been available in the United States for more than 20 years as an aid to stop smoking cigarettes. TNPs, like other nicotine replacement therapies (e.g., gum, lozenges, inhalers, and nasal sprays), provide patients with a source of nicotine that reduces the withdrawal symptoms experienced when smoking is stopped, and particularly the craving brought about by abstinence from cigarettes.

Initially approved for prescription use only, FDA approved Supplemental NDAs for several TNPs in the 1990s to provide for their OTC use for those who are at least 18 years old. Other TNPs were approved initially for OTC use in an original NDA. Today, FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") identifies three marketed OTC TNPs, and two discontinued OTC TNPs:

Currently Marketed OTC TNPs:

- NDA No. 020076 – Novartis Consumer Health, Inc.'s HABITROL (7 mg, 14 mg, and 21 mg nicotine transdermal system) transdermal patch, initially approved on November 27, 1991 for prescription use, and approved for OTC use on November 12, 1999 (S-011);

- NDA No. 020165 – Sanofi-Aventis U.S., LLC's NICODERM CQ (7 mg, 14 mg, and 21 mg nicotine transdermal system) transdermal patch, initially approved on November 7, 1991 for prescription use, and approved for OTC use on August 2, 1996 (S-011); and

- ANDA No. 074612 – AVEVA Drug Delivery Systems. Inc.'s Nicotine Transdermal System, 7 mg, 14 mg, and 21 mg transdermal patch, initially approved on October 20, 1997 for prescription use as a generic equivalent of HABITROL, and subsequently approved for OTC use on October 30, 2007.

Discontinued OTC TNPs:

- NDA No. 020536 – Pharmacia and Upjohn Company's NICOTROL (15 mg nicotine transdermal system) transdermal patch, initially approved on July 3, 1996 for OTC use; however, previously approved on April 22, 1992 under NDA No. 020150 for prescription use; and

- NDA No. 019983 – AVEVA Drug Delivery Systems. Inc.'s PROSTEP (11mg/day and 22mg/day nicotine transdermal system) transdermal patch , initially approved on January 28, 1992 for prescription use, and approved for OTC use on December 23, 1998 (S-012).

Although the various OTC TNPs share a common therapeutic goal – to help patients quit smoking – they achieve that goal through different formulations and product characteristics. Notwithstanding these differences, however, there are certain commonalities among the various OTC TNPs, and, in particular, the currently marketed TNPs. Each TNP is available in various strengths and is applied directly to the skin, usually once daily and typically at the same time each day. Once applied, nicotine is perfused through the skin and into systemic circulation. In addition, each patch, contained in a foil pouch, is a film that adheres to a backing. After use of each TNP, a significant amount of residual drug remains in the used film – approximately 27% to 74% of the total nicotine content in the transdermal patch. Such residual drug content is not unusual. As FDA has explained, "topical patches may retain 10-95 percent of the initial total amount of drug as the residual drug after the intended use period."[1] But, as FDA has noted, such residual drug does raise safety concerns:

> [Residual drug in transdermal drug delivery systems] raises a potential safety issue not only to the patient, but also to others including family members, caregivers, children, and pets. For example, adverse events due to a patient's failure to remove [transdermal drug delivery systems] at the end of the intended use period have been reported and are generally related to an increased or prolonged pharmacological effect of the drug. Also, some children have died from inadvertent exposure to discarded [transdermal drug delivery systems]. Reported adverse events resulting from various quality problems pertaining to [transdermal drug delivery systems] have lead to product recalls, withdrawals, and public health advisories.[2]

The backing membranes of several marketed brand-name TNPs do not have permanent markings identifying the product or otherwise making their respective translucent backing membranes more apparent. This creates a significant risk of misuse or accidental exposure to nicotine, particularly among children. Such risk does not only exist with misuse or accidental pediatric exposure to new and unused TNPs, but

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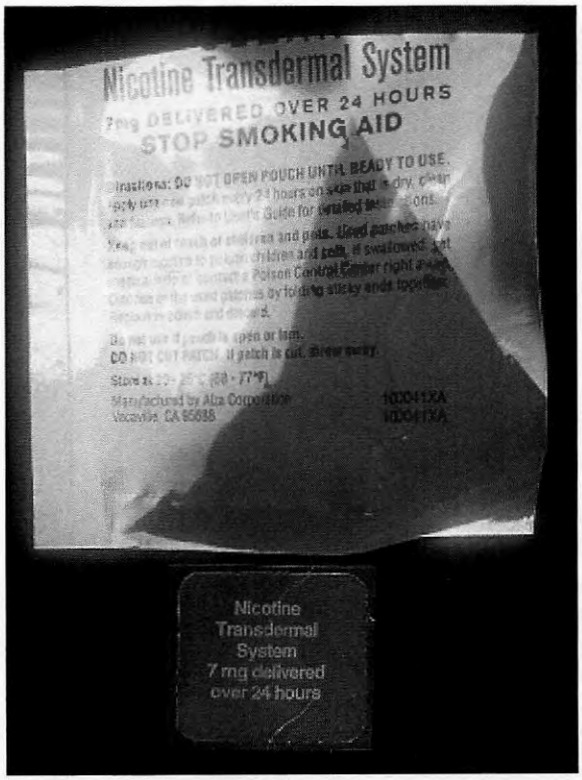
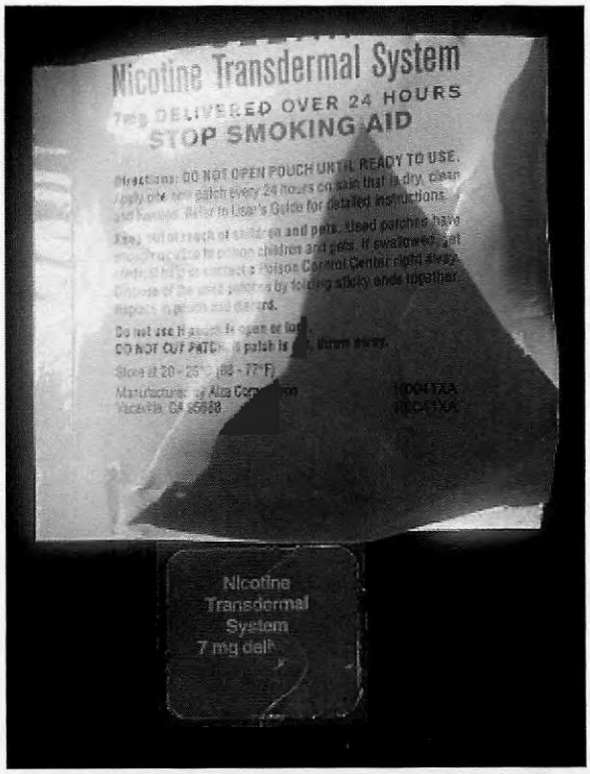
1 FDA, Guidance for Industry: Residual Drug in Transdermal and Related Drug Delivery Systems, at 2 (Aug. 2011).

2 Id.

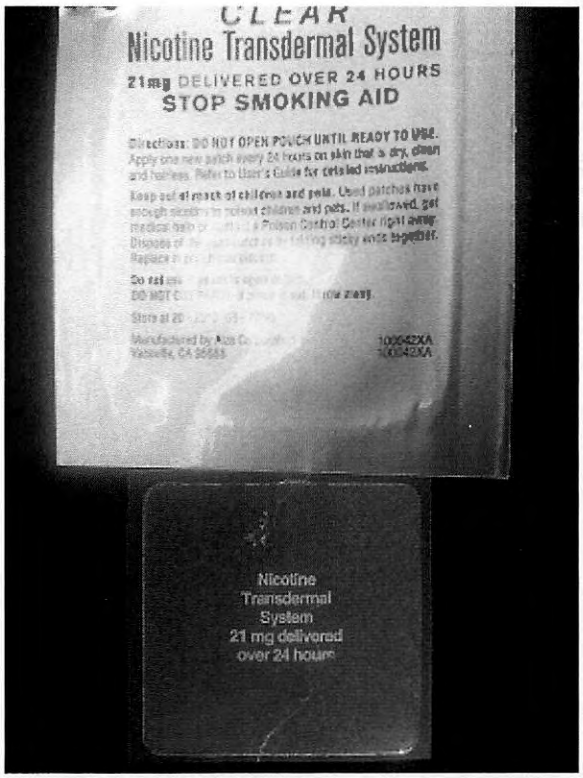
continues to exist after and during TNP use given the high residual amount of nicotine in used TNPs. Pictures of currently marketed brand-name OTC TNPs illustrating the translucent appearance of the transdermal patched are show below and on the following pages.

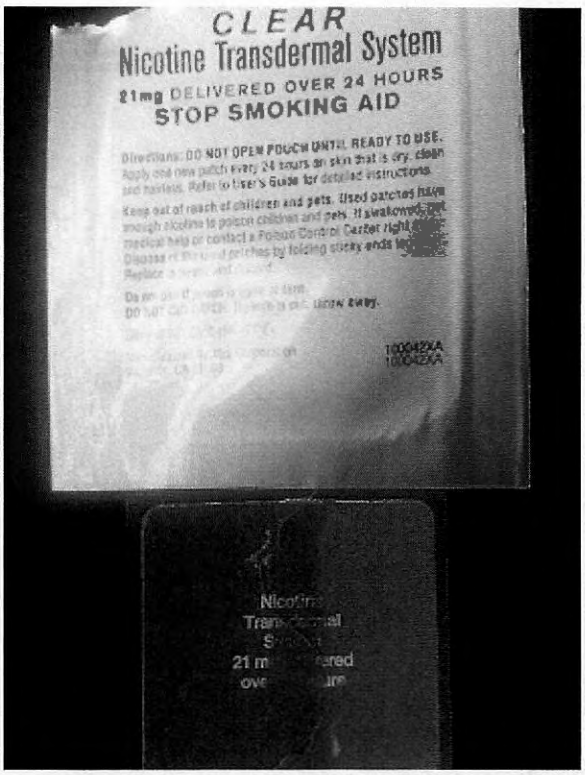
– WALGREEN CLEAR NICOTINE TRANSDERMAL SYSTEM –
(Manufactured By: Alza Corporation)





– NICODERM CQ –
(Manufactured By: Alza Corporation)





– NICODERM CQ –
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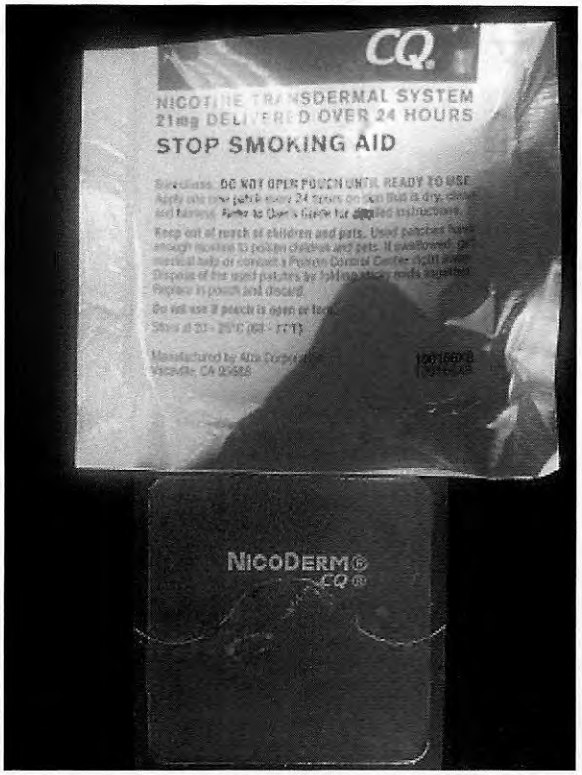

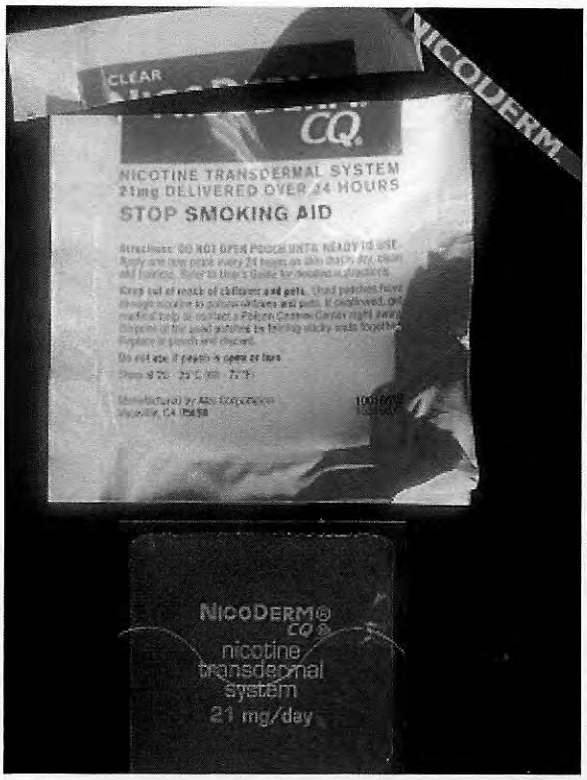

Accidental exposure to the nicotine in OTC TNPs, among other nicotine replacement therapies, can have serious adverse effects, particularly in children. Although the most commonly reported adverse events are minor in nature, such as skin irritation, headache, dizziness, excessive fatigue, nausea and vomiting, some pediatric exposures have required visits to the emergency room. And pediatric nicotine intoxication is a growing problem.

There have been numerous published reports of accidental pediatric nicotine intoxication from TNPs since the products have become more widely available with OTC status.[3] Indeed, in 1997, around the time that many TNPs became available OTC, one

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[3] See, e.g., Woolf A, et al., Childhood poisoning involving transdermal nicotine patches. Pediatrics. 1997 May;99(5):E4 (Attachment No. 1); Wain AA, Martin J., Can transdermal nicotine patch cause acute intoxication in a child? A case report and review of literature. Ulster Med J. 2004 May;73(1):65-6 (Attachment No. 2); Parekh D, et al., Transdermal patch medication delivery systems and pediatric poisonings, 2002-2006. Clin Pediatr (Phila). 2008 Sep;47(7):659-63 (Attachment No. 3).

pediatrician made the prescient prediction that "[a]s the availability of these products increases, it is anticipated that physicians and poison centers will be contacted with increasing frequency concerning inadvertent exposures to them among children."[4] That prediction has been borne out over time.

According to annual reports from the American Association of Poison Control Centers' ("AAPCC") National Poison Data System ("NPDS"), nicotine poisoning from pharmaceutical products, including OTC TNPs, is becoming more prevalent, both in the general United States population, and among children. The most recent annual report from AAPCC/NDPS identifies 1,075 unintentional exposures to nicotine pharmaceuticals. A significant majority of those unintentional exposures were in children: 717 exposures in children 5 years old and younger; 132 exposures in children 6-12 years old.[5] This compares to only 481 unintentional exposures to nicotine pharmaceuticals reported by AAPCC in 1999. The 1999 exposure data show 221 reports concerning nicotine pharmaceuticals in children less than 6 years old, and 80 exposures in children between 6 and 19 years old.[6]

B. FDA Should Require a Permanent, Smudge-Resistant Product Identification on the Backing Membrane of OTC TNP Drug Products

In the past, FDA has requested that holders of applications for approved drug products make labeling changes related to safety to address serious risks. For example, FDA recently notified holders of applications of Fentanyl Transdermal System drug products to make certain appearance changes to avoid accidental pediatric exposure. According to one FDA letter:

> Since Fentanyl Transdermal System was approved, we have become aware of serious adverse event reports of accidental pediatric exposure to fentanyl transdermal systems. Of the 30 accidental pediatric exposures to fentanyl

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4 Woolf A, et al., Childhood poisoning involving transdermal nicotine patches. Pediatrics. 1997 May;99(5):E4, at 1.

5 2011 Annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th Annual Report, 2012 Dec;50(10):911-1164, at 1128, available at https://aapcc.s3.amazonaws.com/pdfs/annual_reports/2011_NPDS_Annual_Report.pdf.

6 1999 Annual Report of the American Association of Poison Control Centers Toxic Exposure Surveillance System, Am J Emerg Med. 2000 Sep;18(5):517-74, at 564, available at https://aapcc.s3.amazonaws.com/pdfs/annual_reports/AJEM_-_AAPCC_Annual_Report_1999.pdf.

> transdermal systems reported to FDA since the time of approval, 26 have resulted in death or hospitalization. Based on the information provided in the reports and our evaluation of the labeling, the FDA has determined that the appearance of fentanyl transdermal systems contributed to the accidental exposures, particularly when the patches became detached, and were subsequently difficult to find and identify, leaving them accessible to be accidentally picked up by a child.
>
> We are requesting that you submit a Combination Prior Approval Supplement to the Agency with a timeline and plan of action for changes that would include established name and strength on the identifying labeling on the backing membrane. Additionally, you should include graphic markings (e.g. lines, stripes) on the backing membrane to increase the visibility of your labeling. All printed matter should be visible throughout the duration of wear. Please also provide any other recommendations for increasing the visibility of the patch. We also request that you include extractables and leachables of new inks utilized, and an assessment of the impact on the inspection system's ability to detect defects due to a change in ink and/or markings on the transdermal system.

Although pediatric exposures to nicotine in OTC TNPs have not resulted in adverse events as serious as those reported for Fentanyl Transdermal System drug products, the number of pediatric exposures to OTC TNP drug products appears to be much greater – and is growing. Given the growing number of unintentional pediatric exposures to OTC TNP drug products and the serious consequences of such exposures, FDA should require labeling changes to address this safety concern. Specifically, FDA should require permanent, smudge-resistant product identification on the backing membrane of OTC TNP drug products to avoid any accidental exposure to nicotine or to help healthcare professionals in emergency situations.

If application holders fail to timely respond to such FDA requests, or if application holders otherwise do not agree with FDA's requested labeling changes, then FDA should initiate proceedings to withdraw approval of the drug on the basis that new safety information "shows that such drug is not shown to be safe for use under the conditions of use upon the basis of which the application was approved." FDC Act § 505(e). Alternatively, FDA could notify the public about the safety information through mechanisms (e.g., Public Health Advisories or notifications on the FDA web site) describing the safety information and the need for labeling changes, or take appropriate

enforcement action on the basis that the absence of the new safety information from labeling renders the drug product misbranded.[7]

III. ENVIRONMENTAL IMPACT

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

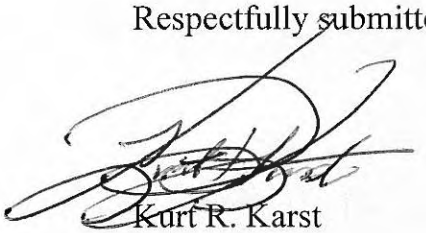
IV. ECONOMIC IMPACT STATEMENT

Petitioner will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

V. 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 Petitioner that are unfavorable to the Petition.

Respectfully submitted,



Kurt R. Karst

Attachments

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[7] Although the statute authorizes FDA to require and, if necessary, order labeling changes if the Agency becomes aware of new safety information that FDA believes should be included in drug product labeling, this authority is limited to prescription drug products. See FDC Act § 505(o)(4).

Rec'd
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Date

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