DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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JUN 4 2015

Kurt R. Karst
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Re: Docket No. FDA-2013-P-1640

Dear Mr. Karst:

This letter responds to the citizen petition dated December 5, 2013 (Petition), that you submitted to the Food and Drug Administration (FDA or Agency). The Petition requests that FDA require the sponsors of all new drug applications (NDAs) for over-the-counter (OTC) transdermal nicotine patches, which we refer to as transdermal delivery systems or TDSs in this response, to include permanent, smudge-resistant, product-identifying labeling on the backing membrane of the OTC nicotine TDSs to help avoid accidental pediatric exposure to nicotine.

All of the currently marketed OTC nicotine TDSs bear markings identifying the product and strength on the backing membrane upon manufacture. You petition is granted insofar as we would consider the products to be misbranded or otherwise in violation of the Federal Food, Drug, and Cosmetic Act to the extent that changes to the required markings might occur under normal conditions of use (e.g., markings rub off or are otherwise not durable).[1] However, our review of the Petition and related evidence does not suggest that pediatric exposure to OTC nicotine TDSs is increasing in frequency, or that the safety risk is such that different or additional markings are necessary on the backing membranes of the products to ensure that their benefits outweigh their risks, and your request that we require changes to the markings on the backing membranes of OTC nicotine TDSs to help avoid accidental pediatric exposure to nicotine is therefore denied.

I. BACKGROUND

Approved nicotine TDSs are stop smoking aids indicated for use to reduce withdrawal symptoms, including nicotine cravings, associated with quitting smoking. There are three currently marketed OTC nicotine TDSs, each of which is available in various strengths.[2]

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[1] To the extent that your Petition requests that FDA "take appropriate enforcement action" (Petition at 8-9), it is denied. Decisions with respect to initiating enforcement action are generally made by the Agency on a case-by-case basis and are within the discretion of the Agency. Requests for the Agency to initiate enforcement actions are not within the scope of FDA's citizen petition procedures (21 CFR 10.30(k)).

[2] The three currently marketed OTC nicotine TDSs are the following: Habitrol, 7 milligrams (mg), 14 mg, and 21 mg, approved for OTC use November 12, 1999 (NDA 020-076); Nicoderm CQ, 7 mg, 14 mg, and

Each nicotine TDS is a film that adheres to a release liner and is packaged in a sealed, protective pouch. To apply the nicotine TDS, a user takes it out of the foil pouch, removes the release liner, and applies it to the skin. The nicotine TDS is applied usually once daily and typically at the same time each day. Once applied, nicotine is perfused through the skin and into systemic circulation. Users are directed to dispose of a used nicotine TDS by folding it in half, sticky sides together, and replacing it in the protective pouch enclosed with the package before throwing it away. Nicotine TDSs have been approved for OTC use since the late 1990s.

As with other TDSs, nicotine TDSs contain a larger amount of the drug substance than what is intended to be delivered to the patient. The excess amount of drug substance is needed to facilitate delivery of the intended amount of the drug to the patient and remains as residual drug in the used TDS. As FDA has recognized, this raises a potential safety issue not only to the patient but also to others, including family members, caregivers, children, and pets.[3] The approved labeling for OTC nicotine TDSs reflects the potential risk by including the following statement: "**Keep out of reach of children and pets.** Used patches have enough nicotine to poison children and pets."[4]

II. DISCUSSION

A. Available Safety Evidence

In the Petition, you claim that accidental exposure to the nicotine in OTC nicotine TDSs "can have serious adverse effects, particularly in children" (Petition at 6). You state that although "the most commonly reported adverse events are minor in nature . . . some pediatric exposures have required visits to the emergency room" (Id.). You also claim that "pediatric nicotine intoxication is a growing problem" (Id.).

1. *Limited Evidence of Serious Adverse Events Related to Pediatric Exposure to OTC Nicotine TDSs*

Although FDA shares your concern about the potential consequences of unintentional exposure to OTC nicotine TDSs, the available evidence does not suggest that accidental pediatric exposure to OTC nicotine TDSs is a safety risk such that different or additional

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21 mg, approved for OTC use August 2, 1996 (NDA 020-165); and nicotine transdermal system, 7 mg, 14 mg, and 21 mg, approved for OTC use October 30, 2007 (ANDA 074-612).

[3] See FDA's guidance for industry, *Residual Drug in Transdermal and Related Drug Delivery Systems*, available on the FDA Drugs guidance Web page at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. FDA's guidance documents, including this guidance, do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations unless specific regulatory or statutory requirements are cited. The use of the word "should" in Agency guidances means that something is suggested or recommended, but not required.

[4] See, e.g., NicoDerm CQ User's Guide, available at http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/020165Orig1s029lbl.pdf.

markings are necessary on the backing membranes of the products to ensure that their benefits outweigh their risks. FDA reviewed the articles cited in the Petition (Petition at 6) and conducted a literature review to assess the evidence of adverse events or poisoning from pediatric exposure to nicotine TDSs. Although cases of pediatric exposure to nicotine TDSs have been reported, most were handled by phone advice or evaluation in an emergency room. Since the products have been approved, no children have died, and only a few serious adverse events have been reported among children, from either dermal or oral exposure to nicotine TDSs.

One study cited in the Petition reviewed reports of 36 exposures to nicotine TDSs in children younger than 16 years old.[5] Half of the cases involved oral exposure and half involved dermal exposure. Of the reported cases, 22 children (61%) suffered no toxic effects from the nicotine TDS exposure. For the other 14 children (39%), symptoms typically were transient and self-limited, and included gastrointestinal complaints, skin irritation, rashes, pallor, lethargy, and irritability. Ten children were referred to an emergency department for observation and management and where treated with supportive care. Only two children were admitted for overnight observation. All of them fully recovered.

Another study cited in the Petition was a retrospective review of the Texas Poison Center Network (TPCN) database from 2002 to 2006 for cases of exposure to TDSs in children younger than 12 years old.[6] Over the 5-year period, TPCN received 110 calls about the exposure of children under the age of 12 to TDSs. Fifteen of those cases involved nicotine TDSs, but no children experienced significant clinical effects as a result of the exposure.

The last study cited in the Petition was a case report involving an 11 year-old boy who was brought to an emergency department in the United Kingdom with nausea, weakness, vomiting, and palpitations.[7] Medical staff found a nicotine TDS on his left upper arm with another mark below it from application the prior day. His vital signs were normal when he arrived at an emergency department, but later, his blood pressure dropped and heart rate slowed, requiring medical intervention. His condition improved over the next several hours, and he was sent home.

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[5] Petition at 6 (citing Woolf, A, et al., May 1997, Childhood Poisoning Involving Transdermal Nicotine Patches, Pediatrics, 99(5):e4) (discussing 33 cases that were reported by U.S. poison control centers between November 1992 and October 1994 and 3 additional cases that were reported to the manufacturer prior to November 1992, all necessarily involving prescription products since the cases were reported before the first nicotine TDS became available OTC).

[6] Petition at 6 (citing Parekh, D, et al., Sept. 2008, Transdermal Patch Medication Delivery Systems and Pediatric Poisonings, 2002-2006, Clin Pediatr (Phila), 47(7):659-663).

[7] Petition at 6 (citing Wain, AA and J Martin, May 2004, Can Transdermal Nicotine Patch Cause Acute Intoxication in a Child? A Case Report and Review of Literature, Ulster Med J, 73(1):65-66).

The other studies identified through FDA's literature search involved either products other than nicotine TDSs or the intentional use of nicotine TDSs by adolescents as part of nicotine replacement therapy.[8] Because these cases do not involve accidental pediatric exposure to OTC nicotine TDSs, they are not relevant to this Petition response.
Both the Petition and FDA identified the American Association of Poison Control Centers' National Poison Data System (AAPCC NPDS) annual reports as a relevant source of information about nicotine poisoning, including nicotine poisoning from exposure to nicotine TDSs. The AAPCC NPDS is a comprehensive poisoning exposure surveillance database containing information submitted from 55 poison centers across the nation. The December 2013 Annual Report identified 1,386 case mentions for "nicotine pharmaceuticals" in 2012.[9] This includes prescription and non-prescription products, as well as different dosage forms of nicotine pharmaceuticals (e.g., TDS, gum, and lozenge). Most of the nicotine pharmaceutical exposures were unintentional (1,041), and about half, 672, were in children ages 5 or younger. For all nicotine pharmaceutical case mentions, there were no deaths, 2 "major" outcomes, and 34 "moderate" outcomes reported.[10] The AAPCC NPDS provides information on nicotine pharmaceuticals in the aggregate, so there is no way to know how many of the cases mentioned involved OTC nicotine TDSs as opposed to gum or lozenges and whether any of the major or moderate outcomes involved nicotine TDSs.

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[8] Two studies involved products other than OTC nicotine TDSs. See Connolly, GN, et al., May 2010, Unintentional Child Poisonings Through Ingestion of Conventional and Novel Tobacco Products, Pediatrics, 125(5):896-899 (tobacco products); Hamblin, JE and CA Martin, Jan. 1987, Transdermal Patch Poisoning, Pediatrics, 79(1):161 (case report involving a clonidine patch). Three other studies involved the intentional use of nicotine TDSs, and other nicotine pharmaceuticals, as part of nicotine replacement therapy for adolescent smokers. See Price, JH, et al., Apr. 2007, Pediatricians' Use of the 5 A's and Nicotine Replacement Therapy With Adolescent Smokers, J Community Health, 32(2):85-101; Moolchan, ET, et al., Apr. 2005, Safety and Efficacy of the Nicotine Patch and Gum for the Treatment of Adolescent Tobacco Addiction, Pediatrics, 2005 Apr; 115(4):e407-414; Smith, TA, et al., Oct. 1996, Nicotine Patch Therapy in Adolescent Smokers, Pediatrics, 98(4 Pt 1):659-667.

[9] Mowry, JB, et al., Dec. 2013, 2012 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 30th Annual Report, Clin Toxicol (Phila), 51(10): 949-1229. As a point of comparison, the same report included 9,107 case mentions for tobacco or nicotine products (e.g., chewing tobacco, cigarettes, or electronic cigarettes) during the same time period. Id.

[10] For purposes of the AAPCC NPDS, a "major" outcome is one in which the "patient exhibited signs or symptoms as a result of the exposure that were life-threatening or resulted in significant residual disability or disfigurement (e.g., repeated seizures or status epilepticus, respiratory compromise requiring intubation, ventricular tachycardia with hypotension, cardiac or respiratory arrest, esophageal stricture, and disseminated intravascular coagulation)." Supra note 9. The AAPCC NPDS defines a "moderate" outcome as one in which the "patient exhibited signs or symptoms as a result of the exposure that were more pronounced, more prolonged, or more systemic in nature than minor symptoms. Usually, some form of treatment is indicated. Symptoms were not life-threatening, and the patient had no residual disability or disfigurement (e.g., corneal abrasion, acid – base disturbance, high fever, disorientation, hypotension that is rapidly responsive to treatment, and isolated brief seizures that respond readily to treatment)." Id.

In addition to its literature search and analysis of the AAPCC NPDS data, FDA also searched the FDA Adverse Event Reporting System (FAERS)[11] and the National Electronic Injury Surveillance System, Cooperative Adverse Drug Event Surveillance (NEISS-CADES) database[12] for cases of accidental pediatric exposure to OTC nicotine TDSs. Between November 1999 and March 2014, one case of accidental pediatric exposure to an OTC nicotine TDS was reported in FAERS. In that case, which occurred in 2004, a 13-month-old child was put to bed by the child's grandmother. At 11:30 p.m., the grandmother noticed that her nicotine TDS had detached, and at 1:45 a.m., the child woke up vomiting. The child's mother found the nicotine TDS on the child's skin under his shirt. The child was taken to an emergency room and admitted for observation and monitoring. Similarly, between 2004 and 2012, one case of an emergency department visit by a child under 18 years of age involving a nicotine TDS was reported in the NEISS-CADES database.[13] In 2006, a 21-month-old child accidentally ingested (chewed) a nicotine TDS. A physician treated and released the child from the emergency department.

The evidence described above does not suggest that accidental pediatric exposure to OTC nicotine TDSs poses a safety risk such that different or additional markings on the backing membranes of these products are necessary to ensure that the benefits outweigh the risks.

2. No Evidence of Increasing Prevalence

You also claim that permanent and prominent markings should be required on OTC nicotine TDSs because the number of pediatric exposures to OTC nicotine TDSs "is growing" (Petition at 8). You cite data from the AAPCC NPDS annual reports and note the increase in unintentional exposures to nicotine pharmaceuticals between 1999 and 2011 (Petition at 7).[14]

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[11] FAERS, formerly the Adverse Event Reporting System (AERS), is a database that contains information about adverse event and medication error reports submitted to FDA. FDA moved data from AERS to FAERS for the launch of FAERS on September 10, 2012.

[12] The NEISS-CADES data source provides data from a stratified probability sample of 63 U.S. hospitals with a minimum of six beds and a 24-hour emergency department. The data represent only patients who went to an emergency room and reported exposure to the drug.

[13] In addition to the one case involving a nicotine TDS, during the same time period, there were 6 cases involving a nicotine lozenge, 21 cases involving nicotine gum, and 4 cases involving e-cigarette liquid reported in the NEISS-CADES database.

[14] You claim that a "significant majority" of these unintentional exposures were in children. However, the AAPCC NPDS annual reports categorize all unintentional exposures together, regardless of whether in children or adults, so there is no way to know how many of the unintentional exposures involved children. Although children, especially young children, are less likely to use nicotine pharmaceuticals intentionally, there are studies on the use of nicotine TDSs as nicotine replacement therapy for adolescents. See Moolchan, ET, et al., Apr. 2005, Safety and Efficacy of the Nicotine Patch and Gum for the Treatment of Adolescent Tobacco Addition, Pediatrics, 115(4):e407-14; Smith, TA, et al., Oct. 1996, Nicotine Patch Therapy in Adolescent Smokers, Pediatrics, 98(4 Pt 1):659-667.

Although there were more reports of unintentional exposure to nicotine pharmaceuticals in 2011 than in 1999 in the AAPCC NPDS, FDA disagrees that there is evidence that accidental pediatric exposure to OTC nicotine TDSs is a growing problem. First, the three most recent annual reports (for years 2010 to 2012) show a stable number of exposure calls related to nicotine pharmaceuticals received at poison controls centers, not an increase (1,231 calls in 2010, 1,310 calls in 2011, and 1,272 calls in 2012). In addition, as noted above, the AAPCC NPDS data on nicotine pharmaceuticals does not distinguish between different product formulations (e.g., TDS, lozenge, or gum), or in prescription versus OTC status. Thus, there is no way to confirm from the AAPCC NPDS annual reports how many unintentional exposures are from OTC nicotine TDSs as opposed to from other nicotine pharmaceuticals.

In addition, retail sales data from the IMS Health OTC International Market Tracking (OTCIMS) database do not provide evidence of increased overall distribution or availability of nicotine TDSs over recent years. Although the extent of exposure to the pediatric population cannot be determined from retail sales data, sales of OTC nicotine TDSs held steady or declined from 2010 through 2012. As noted above, although exposure calls related to all types of nicotine pharmaceuticals received at poison control centers also were steady during this time period, sales of other OTC nicotine replacement therapies (e.g., gum) increased during this same time frame.[15]

The available evidence does not suggest that nicotine poisoning from accidental pediatric exposure to OTC nicotine TDSs is becoming more prevalent or poses a safety risk such that different or additional markings on the backing membranes are necessary to ensure that the benefits of the products outweigh the risks.[16]

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[15] IMS Health, OTC International Market Tracking (OTCIMS). Years 2007-2013. Data extracted March 2014. Between 2007 and 2010, overall retail sales of nicotine replacement therapy, regardless of product formulation, declined from 7 million packages to 4.9 million packages. However, between 2010 and 2013, overall retail sales increased 28% from 4.9 million packages to 6.3 million packages. Most of the increase between 2010 and 2012, however, is attributable to nicotine gum products and, to a lesser extent, lozenges. In 2011, 100,000 fewer packages of nicotine TDSs were sold than in 2010, and the sales for 2011 and 2012 were nearly identical. Sales of nicotine TDSs also declined in 2013 by about 50,000 packages.

[16] In urging FDA to grant your request, the Petition cites to the Duragesic (fentanyl) pain TDSs, where FDA required specific changes to the markings on the backing membrane to make the markings more prominent to help prevent accidental exposure to the product (Petition at 7-8). Exposure to fentanyl TDSs posed a very significant safety risk for children, with most of the reported cases of pediatric exposure involving serious harm that resulted in death or required hospitalization and medical intervention. See FDA Drug Safety Communication, *FDA Requiring Color Changes to Duragesic (Fentanyl) Pain Patches to Aid Safety—Emphasizing That Accidental Exposure to Used Patches Can Cause Death*, Sept. 23, 2013, available at http://www.fda.gov/Drugs/DrugSafety/ucm368902.htm. Given the vastly greater safety risk involved in the regulation of fentanyl TDSs, we do not believe the fentanyl precedent informs our response to this Petition.

B. Labeling of Currently Marketed OTC Nicotine TDSs

You claim that the lack of permanent and prominent markings on the backing membranes of OTC nicotine TDSs "creates a significant risk of misuse or accidental exposure to nicotine, particularly among children" (Petition at 3). You provide no support for this assertion, and it cannot be inferred from the available evidence, which does not describe the role, if any, that TDS identification (or the lack thereof) contributes to accidental pediatric exposure to OTC nicotine TDSs. In any case, all of the currently marketed OTC nicotine TDSs bear markings identifying the product and strength on the backing membrane upon manufacture. To the extent that changes to the required markings might occur under normal conditions of use (e.g., markings rub off or are otherwise not durable), we would consider the products to be misbranded or otherwise in violation of the Federal Food, Drug, and Cosmetic Act. The Agency intends to work with the sponsors of OTC nicotine TDSs as appropriate to ensure that the required markings comply with the Act. However, our review of the Petition and related evidence does not suggest that pediatric exposure to OTC nicotine TDSs is increasing in frequency, or that the safety risk is such that different or additional markings are necessary on the backing membranes of the products to ensure that their benefits outweigh their risks.

IV. CONCLUSION

For the reasons set forth above, the Petition is granted in part and denied in part.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research