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August 1, 2000

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1-23
12420 Parklawn Dr.
Rockville, MD 20857

Re: Citizen Petition For Nicotine Product Pregnancy Warning Language

Dear Sir or Madam:

On behalf of Paul Dowhal ("Petitioner"), a resident of the State of California, the undersigned submits this Petition under the Federal Food Drug and Cosmetic Act 21 U.S.C. §§321 *et seq.* (the "FDCA") and the Administrative Procedures Act, 5 U.S.C. §553(e) (the "APA") to request the Commissioner of the Food and Drug Administration ("FDA") to change the pregnancy nursing warning on certain OTC nicotine replacement products, including nicotine gum and nicotine patches ("Nicotine Products"), from the current "increased heart rate" warning to a warning that more broadly communicates all of the potential reproductive harm associated with nicotine use. The detailed grounds for this Petition are set forth below.

A. Action Requested:

Petitioner requests that the Commissioner require a consistent pregnancy warning for use with all Nicotine Products. This warning should not be limited to one particular effect associated with maternal nicotine exposure, such as increased fetal heart rate. The warning should broadly communicate to pregnant women that use of nicotine, whether from smoking or medication, can harm the baby, and that pregnant women should first try to stop smoking without using the nicotine product. This warning may be effectuated by a class labeling requirement or otherwise as the Commissioner sees fit.

B. Statement of Grounds:

(1) The "Increased Heart Rate" Warning Currently Approved For Use On Many Nicotine Products Fails To Communicate Adequately The Known Reproductive Harms Caused By Nicotine

Nicotine has been shown in animal studies to cause severe reproductive harm.

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Recognizing this fact, FDA originally classified prescription nicotine products as Category X - not for use by pregnant women. In addition, FDA acknowledged that nicotine is known to cause reproductive harm by requiring the following warning language for use with various prescription Nicotine Products:

- Nicotine has been shown in animal studies to cause fetal harm. It is therefore presumed that [the Prostep Nicotine Patch] can cause fetal harm when administered to pregnant women. (Prostep Nicotine Patch prescription warning).

- Nicotine was shown to produce fetal skeletal abnormalities in the offspring of mice. (Nicotrol NS Nasal Spray prescription warning).

- Nicotine from any source can be toxic and addictive. (Nicotrol NS Nasal Spray and Habitrol nicotine patch prescription warning).

- Spontaneous abortion during nicotine replacement therapy has been reported; as with smoking, nicotine as a contributing factor cannot be excluded. (Nicotrol Inhaler prescription warning).

- If Nicotrol NS is used during pregnancy, ...the patient should be apprized of the potential hazard to the fetus. (Nicotrol NS prescription warning).

- Do not use if you are pregnant (or think you may be pregnant) or nursing unless your doctor tells you to do so. Nicotine in any form can cause harm to your unborn baby. (Nicotrol Inhaler prescription warning).

Recent studies have confirmed these findings as well as the fact that nicotine itself, without the other constituents of tobacco smoke, is a neuroteratagen that: (1) causes cellular damage and reduced cell number in the fetal brain; (2) impairs synaptic activity; and (3) evokes these changes at thresholds below those required for maternal toxicity, fetal growth impairment, or other overt signs of systemic toxicity.[1] In addition to fetal brain damage, recent

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[1] *See* [1] Levin, E.D. and Slotkin, T.A., Developmental Neurotoxicity of Nicotine, in W. Slikker and L.W. Chang (Eds.), Handbook of Developmental Neurotoxicology, pp. 587-615, Academic Press, San Diego, 1998; [2] Slotkin, T.A., Fetal Nicotine or Cocaine Exposure: Which One Is Worse?, J. Pharmacol. Exp. Ther. 285 (1998) 931-945; [3] Slotkin, T.A., Developmental Cholinotoxicants: Nicotine and Chlorpyrifos, Environm. Hlth. Perspect. 107 (1999) Suppl. 1, 71-80; [4] Roy, T.S. and Sabherwal, U., Effects of Prenatal Nicotine Exposure on the Morphogenesis of Somatosensory

literature demonstrates that maternal nicotine exposure causes disturbances in respiratory function that may predispose infants to SIDS[2], causes adverse effects on lung development[3], and causes a reduction in placental transport of nutrients to the fetus.[4][5]

In stark contrast to the warnings required by FDA for prescription nicotine products, which clearly communicate that nicotine can cause a multitude of serious reproductive harms, the current warning approved by FDA for certain Nicotine Products, such as the widely marketed Nicoderm CQ nicotine patch, the Nicotrol nicotine patch and various store brand nicotine patches, reads as follows:

> Nicotine can increase your baby's heart rate. First try to stop smoking without the nicotine patch. As with any drug, if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

The current warning approved by FDA for nicotine gums, such as Nicorette and its generic counterpart, reads as follows:

Cortex, Neurotoxicol. Teratol. 6 (1994) 411-421; [5] Roy, T.S. and Sabherwal, U., Effects of Gestational Nicotine Exposure on Hippocampal Morphology, Neurotoxicol. Teratol. 20 (1998) 465-473.

[2] *See* [1] Milerad, J. and Sundell, H., Nicotine Exposure and the Risk of SIDS, Acta Pædiat. Suppl. 389 (1993) 70-72; [2] Hafstrom, O., Milerad, J., Asokan, N., Poole, S.D. and Sundell, H.W., Nicotine Delays Arousal During Hypoxemia in Lambs, Pediatr. Res. 47 (2000) 646-652; [3] Milerad, J., Larsson, H., Lin, J. and Sundell, H.W., Nicotine Attenuates the Ventilatory Response to Hypoxia in the Developing Lamb, Pediatr. Res. 37 (1995) 652-660.

[3] *See* Schuller, H.M., Jull, B.A., Sheppard, B.J. and Plummer, H.K., Interaction of Tobacco-Specific Toxicants with the Neuronal or, Nicotinic Acetylcholine Receptor and its Associated Mitogenic Signal Transduction Pathway: Potential Role in Lung Carcinogenesis and Pediatric Lung Disorders, Eur. J. Pharmacol. 393 (2000) 265-277.

[4] *See* Ganapathy, V., Prasad, P.D., Ganapathy, M.E. and Leibach, F.H., Drugs of Abuse and Placental Transport, Adv. Drug Deliv. Rev. 38 (1999) 99-110.

[5] It is Petitioner's understanding that all of the references included in this Petition have been submitted to FDA in connection with this proceeding. Should that not be the case, copies of any such references will be provided.

> Nicotine can increase your baby's heart rate; if you are pregnant or nursing a baby, seek the advice of a health professional before using this product.

These warnings do not even mention the word harm. They simply refer to an increased fetal heart rate, which does not necessarily communicate harm or danger. Indeed, most lay people believe that exercise increases heart rate and that exercise is a healthy activity, particularly for pregnant women. Accordingly, many lay people may reasonably believe that an increased baby's heart rate poses no risk whatsoever.

More importantly, the known data about the serious reproductive harm that nicotine causes and that continues to be demonstrated in published studies, including fetal brain and lung damage, is simply left out of the "increased heart rate" warning. In fact, the Nicorette warning, fails to even suggest to users that they first try to stop smoking without the Nicotine Product. The absence of the suggestion implies that such products are as safe as abstinence, and provides no incentive for pregnant women who may consider attempting to quit smoking without use of nicotine in any form to do so. Consequently, the "increased heart rate" warning currently approved for most Nicotine Products does not "enable consumers to better read and understand the information presented and apply this information to the safe and effective use of OTC drug products," and thus fails to meet the mandate of the FDCA. *See* 64 Fed. Reg. 13254.

(2) The "Harm Your Baby" Warning Recently Approved For Use On the Habitrol OTC Nicotine Product Clearly And Reasonably Communicates The Known Reproductive Harms Caused By Nicotine.

In contrast, FDA recently approved the Habitrol nicotine patch product for OTC sale with a pregnancy warning that differs markedly from the warnings described above which continue to appear on ostensibly identical OTC Nicotine Products. The Habitrol warning reads as follows:

> If pregnant or breast-feeding, ask a health professional before use. Nicotine, whether from smoking or medication, can harm your baby. First try to stop smoking without the patch.

Unlike the "increased heart rate" warning, the "harm your baby" warning approved for Habitrol broadly encompasses the full range of known reproductive harms caused by nicotine, and does so in a clear and easily understood fashion. Furthermore, by disclosing that nicotine — whether from smoking or medication — can harm the fetus, with an admonition to try to stop smoking without the patch, the Habitrol warning accurately and fairly quantifies the varying degrees of harm between use of Habitrol and total abstinence. As a result, the Habitrol warning,

unlike the "increased heart rate" warning which fails to communicate any discernible reproductive harm, is likely to encourage pregnant consumers for whom total abstinence is a realistic alternative to attempt to quit smoking without the use of nicotine in any form. Accordingly, Petitioner requests that the Commissioner require that all Nicotine Products display a pregnancy warning that clearly and reasonably communicates all of the known reproductive harms of nicotine rather a warning limited to one known effect (increased fetal heart rate). The Habitrol OTC pregnancy warning is one example of such a clear and reasonable warning.

(3) In A Proposition 65 Lawsuit Against The Makers Of The Nicotine Products, Petitioner Has Been Advocating A Pregnancy Warning Substantially Similar To The Habitrol "Harm Your Baby" Warning.

As your office is aware, on March 20, 1998, Petitioner filed a Notice of Violation of the California Safe Drinking Water and Toxic Enforcement Act of 1986 ("Proposition 65") against the companies involved in the development, approval, sale and marketing of OTC Nicotine Patches and Nicotine Gum, alleging that the "increased heart rate" warning displayed on such Nicotine Products fails to clearly and reasonably communicate the known reproductive harms of nicotine, in violation of Proposition 65. After eighteen months of failed negotiations with the manufacturers of the Nicotine Products, Petitioner filed an enforcement action in San Francisco Superior Court (*Dowhal v. SmithKline Beecham Consumer Healthcare, LP, et al.*; Case No. 305893) on August 23, 1999. The lawsuit seeks injunctive relief consisting of clear and reasonable warnings regarding the reproductive toxicity of nicotine as well as civil penalties and restitution.

In approving Proposition 65 in 1986, California voters declared their right "to be informed about exposures to chemicals that cause...reproductive harm." Proposition 65, Sec. 1(b), Nov. 4, 1986. Accordingly, the overall objective of Petitioner's Proposition 65 suit is not to scare consumers or dissuade them from taking steps to quit smoking, but rather to ensure that pregnant and breast-feeding consumers are able to make an "informed" decision when they choose to use Nicotine Products. Specifically, Petitioner seeks to require a pregnancy warning that, unlike the "increased heart rate" warning, clearly and reasonably quantifies the relative reproductive harms of smoking, use of the Nicotine Products and total abstinence from nicotine such that consumers for whom total abstinence during pregnancy is a realistic option will understand that abstinence is indeed the safest alternative.

While Proposition 65 provides "safe harbor" warning language, the statute expressly states that any "clear and reasonable" warning is compliant. California Health and Safety Code §25249.11(f), and 22 California Code of Regulations §12601(a). In connection with his Proposition 65 action, Petitioner has consistently taken the position that given the unique harm associated with smoking and pregnancy, this case particularly justifies the use of a unique

warning. Accordingly, Petitioner has, since the initiation of this legal action in 1998, publicly advocated a "harm your baby" warning in combination with an admonition to first try to stop smoking without the Nicotine Product. This warning is nearly identical to the Habitrol warning approved by FDA.

(4) Requiring A "Harm Your Baby" or Similar Warning On All OTC Nicotine Products Achieves Compliance With Both The FDCA And Proposition 65.

At the insistence of Petitioner, certain sponsors of the Nicotine Products other than Habitrol have themselves approached FDA to inquire about use of the Habitrol warning on their products. In part as a result of Petitioner's enforcement action, it is our understanding that FDA is currently reconsidering the pregnancy warning for Nicotine Products. Consequently, Petitioner strongly urges FDA to require that all Nicotine Products employ a warning that more broadly communicates the known harm associated with nicotine. The Habitrol pregnancy warning, currently approved by FDA, is one example of such a warning. Requiring such a warning will not only achieve consistent warnings across a class of substantially identical OTC drug products, but will also harmonize the requirements of the FDCA and Proposition 65 as applied to the Nicotine Products. Indeed, such harmonization was precisely what Congress envisioned when it expressly exempted Proposition 65 from the broad state preemption provisions in the FDCA Modernization Act. 21 U.S.C. §379r(d)(2). As FDA has made clear its intent to defer to Congressional mandate on this issue,[6] requiring the Habitrol "harm your baby" warning or another similar warning on all OTC Nicotine Products constitutes a simple and straightforward solution.

C. Environmental Impact

As required by 21 C.F.R. §10.30, Petitioner states that the actions requested by this Petition fall within the categorical excl
usion from the environmental assessment requirements of the National Environmental Policy Act under 21 C.F.R. §§25.30(k) and 25.31.

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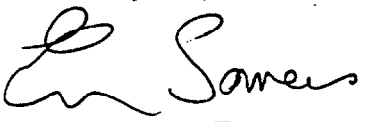
[6] When FDA finalized its new OTC drug labeling regulations in 1999 in the wake of the Modernization Act, the agency removed the broad preemptive language that had appeared in the proposed rule, and instead stated that, with respect to state initiatives like Proposition 65, "this final rule will, at this time, rely on the terms of the statute in addressing preemption issues." 64 Fed. Reg. 13254.

D. 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, to the extent applicable, representative information known to the Petitioner which is unfavorable to the Petition.

Yours very truly,



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