The attached document represents CTP's then-current thinking on certain aspects of tobacco regulatory science. The information contained herein is subject to change based on advances in policy, the regulatory framework, and regulatory science, and, is not binding on FDA or the public. Moreover, this document is not a comprehensive manual for the purposes of preparing or reviewing tobacco product applications. FDA's review of tobacco product applications is based on the specific facts presented in each application, and is documented in a comprehensive body of reviews particular to each application.

Given the above, all interested persons should refer to the Federal Food, Drug, and Cosmetic Act, and its implementing regulations, as well as guidance documents and webinars prepared by FDA, for information on FDA's tobacco authorities and regulatory framework. This document does not bind FDA in its review of any tobacco product application and thus, you should not use this document as a tool, guide, or manual for the preparation of applications or submissions to FDA.

MEMORANDUM

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Date: 2015.08.24 08:36:57 -04'00'

Date: June 10, 2015

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Division of Nonclinical Science, Office of Science

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Date: 2015.08.24 09:39:19 -04'00'

Kimberly Benson, PhD
Director
Division of Nonclinical Science, Office of Science

To: File

Subject: SE Review: Use of Propylene Glycol in Smokeless Tobacco Products

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Purpose

Propylene glycol (PG) is a common ingredient in smokeless tobacco products. This memo reflects the current view of the CTP's Office of Science/ Division of Nonclinical Science (DNCS) on the science regarding propylene glycol, specifically as it relates to the use in smokeless tobacco products and focuses on its potential role as a permeability enhancer, which may have an impact on the absorption and bioavailability of HPHCs and cause the new product to raise different question in public health.

Background--Propylene Glycol as a permeability enhancer

PG is used as a food additive and in commercial formulations of drugs and cosmetics. PG is considered Generally Recognized as Safe (GRAS) by the FDA (21 C.F.R. 184.1666) in food. The health effects of PG on oral, dermal, and respiratory exposure (short (i.e., airway irritation) and long term (i.e., asthma)) have been well documented (http://www.atsdr.cdc.gov/toxprofiles/tp189.pdf) (Wieslander *et al.*, 2001;Vardavas *et al.*, 2013;Choi *et al.*, 2010). However, the levels of PG typically present in oral tobacco are below toxic levels via the oral route. Instead, it is the wide use of PG as a penetration enhancer to assist drug absorption and delivery in topical pharmaceutical formulations either individually or in combination with other agents for a synergistic effect (i.e., fatty acids, alcohols) (Karande & Mitragotri, 2009) that creates toxicological concern over the addition of PG to oral tobacco products. PG exerts its permeability enhancing role through various mechanisms in drug delivery systems. Some of the data for this permeation

enhancement comes from studies of transdermal drug transfer. While studies on the role of propylene glycol in dermal drug transfer elucidate relevant mechanisms of action, these studies are also likely to underestimate the effect of PG on drug transfer across the oral mucosa, since this tissue, including the buccal membrane, is more permeable than the dermis (Squier and Hall, 1985; Squier et al., 1986; Lesch et al., 1986).

Permeation of PG through tissues can alter thermodynamic activity of many hydrophilic, as well as lipophilic, drug formulations (e.g., antiestrogens, hydrocortisone), changing their diffusion properties (Godwin et al., 1999; Funke et al., 2002). In addition, PG influences intercellular lipid packing within the stratum corneum bilayers resulting in reduced drug–tissue binding and enhanced drug transfer (Ahad *et al.*, 2009;Williams & Barry, 2004;Barry & Bennett, 1987). In a study investigating *in vitro* percutaneous permeation of loperamide hydrochloride in formulations containing PG, a correlation was found between the amount of PG applied on the skin and the amount of drug that had permeated (Trottet *et al.*, 2004). PG was also found to alter the solubility of ibuprofen in the stratum corneum barrier in a manner proportional to its level in the formulation (Herkenne *et al.*, 2007). Regarding mucosal drug delivery, the best topical delivery of phenylephrine to the oral mucosa was achieved with the use of a vehicle containing PG (Soref & Fahl, 2015). In addition, the delivery of fluconazole, an antifungal drug, from bioadhesive buccal gels was found increased with PG as compared to other tested absorption enhancers (Suresh & Manhar, 2014). PG can also work synergistically with other permeation enhancers to increase the transdermal permeability of drugs in the formulations, possibly by increasing perturbation of mucosal barrier integrity and loss of stratum corneum lipids . For example, transdermal permeation of naloxone, an opioid antagonist, was found above therapeutically relevant concentrations when a mixture of PG/ethanol was used as a vehicle (Panchagnula *et al.*, 2001).

There are several studies looking at how PG might affect the absorption or bioavailability of a number of different drugs across skin in both laboratory animals and humans, as well as across the buccal membrane. A few studies have shown that PG can also be an effective permeation enhancer at lower concentrations similar to those present in oral tobacco (e.g., 5%). When the effect of PG as a permeation enhancer on the release of clotrimazole transdermal spray was investigated at two different concentrations (3% and 5% v/v), 3% PG was found to be more effective in enhancing the in vitro drug release through rat skin (Paradkar *et al.*, 2015). In another study investigating release of aceclofenac (a non-steroidal anti-inflammatory drug) from different gel formulations, permeation of aceclofenac was increased with the addition of PG and formulations containing 5% PG showed higher flux (permeability and drug release) values compared to other formulations (Patel *et al*., 2011). For fenretinide, an extremely hydrophobic chemopreventive compound with poor tissue permeability, co-incorporation of 5-10 wt% PG in fenretinide/Eudragit® RL PO patches led to significant enhancement ($p < 0.001$) in the rate and extent of fenretinide permeation across porcine buccal mucosa. After co-incorporation of 5% and 10% PG, the flux of fenretinide was increased by 1.6 and 2.3-fold respectively compared to the permeation enhancer-free patches. Fenretinide content in the buccal tissue after 12 h of ex vivo permeation also increased from 43.8 ± 6.1 µg fenretinide/g tissue in control

(permeation enhancer-free patch) to 158.5 ± 4.7 µg/g in patches with 5% PG and 170.7 ± 5.3 µg/g in patches with 10% PG (Wu et al., 2013).

Further, a United States Patent (US 6319913 B1) lists a glycol component, including PG, as part of a permeation enhancing system in a topical transdermal drug delivery system that can also be applied to tablets designed to deliver drugs via the buccal and sublingual routes (http://www.google.co.in/patents/US6319913). In summary, this information supports the potential for permeation enhancement due to PG as an ingredient in tobacco products.

PG in tobacco products

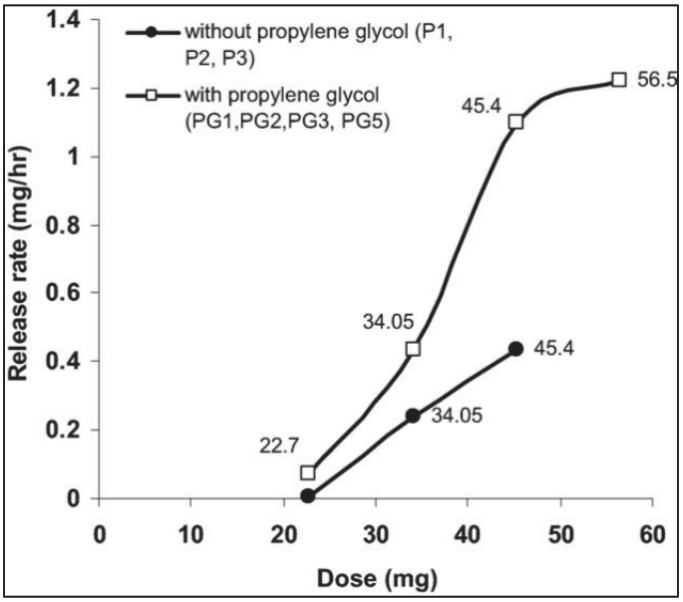
In the vast majority of SE Reports DNCS has reviewed to date, PG has been listed as an ingredient in smokeless tobacco products. A search of CTP IMAGE using the key words "propylene glycol" and "smokeless" in the "advanced search" function and restricting the search to SE Report resulted in 1953 hits (accessed 7/6/2015). While the function of PG in oral tobacco products is often listed as "humectant" in SE Reports, PG may also enhance absorption of nicotine and other more toxic constituents in tobacco products. This conclusion is based on a several lines of evidence, including the information about PG and its use in increasing drug absorption or bioavailability. It is also based on the fact that there is a United States Patent application for smokeless tobacco products which describes PG as a "substance that enhances absorption through buccal and gingival mucosa epithelium for the delivery of drugs and chemicals" (https://www.google.com/patents/US20100242978). In addition, there is a study investigating the transdermal release of nicotine from a membrane-controlled transdermal system. This study used varying amounts of nicotine in the gel reservoir with or without PG. Three groups for both the control (without PG) and PG gels without transfer adhesive were tested, with a low, mid and high level dose of nicotine. An additional dose group included the high dose nicotine in PG and commercial Nicotinell, which showed that the fluxes of nicotine from both of them were close to the *in vitro* target release rate. The researchers measured the amount of nicotine being transported across the membrane and found that this amount increased about 2-10 fold in a gel reservoir containing PG (PG1-PG3, and PG5, see details in the Table 1 and Figure 1 below) compared to the gel reservoir without PG (P1-P3)(Tirnaksiz & Yuce, 2005). These results could be due to PG's potential to enhance penetration.

Table 1. Kinetic assessment of release profiles for transdermal formulation (TFs) (20 cm^2) and nicotine in a commercial product (Nicotinell, 52.5 mg/30 cm^2) [13]

Code	Release rate (mg h^{-1})	R^2
P1 (22.7 mg nicotine)	**0.0071**	0.964
P2 (34.05 mg nicotine)	0.242	0.901
P3 (45.4 mg nicotine)	0.435	0.800
PG1 (22.7 mg nicotine)	**0.071**	0.917
PG2 (34.05 mg nicotine)	0.437	0.984
PG3 (45.4 mg nicotine)	1.1	0.861
PG5 (56.5 mg nicotine)	1.22	0.935
Nicotinell (52.5 mg nicotine, 30 cm^2)	1.08	0.873
	0.361 [a]mg $h^{-1/2}$	
Target release rate	1.07	1

[a] Calculated according to matrix kinetics (mg $h^{-1/2}$)

Figure 1. The relationship between the release rate of nicotine and the drug loading amount in the gel reservoir in a transdermal system [13]



Summary

Evidence supports a role for PG as a penetration enhancer in topical pharmaceutical formulations. Additional evidence supports that this effect of PG could also occur across the buccal membrane. Extensive use of PG in smokeless tobacco products raises the concern about its potential influence on bioavailability of HPHCs such as nicotine, NNN and NNK. Moreover, while data demonstrating PG's permeability enhancement of drugs and chemicals across the dermis can elucidate important mechanisms; this data is likely to underestimate the effect of PG on the absorption of tobacco constituents across the oral mucosa, including the buccal membrane. The Division will take this evidence into consideration in the review of smokeless tobacco products containing PG and will continue collecting information about its influence on mucosal permeability.

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