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.

U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: Division of Product Science

From: Megan Schroeder, Ph.D.
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Office of Science, CTP

Digitally signed by Megan J. Schroeder -S
Date: 2019.07.08 13:38:32 -04'00'

Through: Iilun Murphy, M.D.
Director, Division of Individual Health Science
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Date: 2019.07.08 13:44:13 -04'00'

Subject: BCP Reviews of SE Reports Involving Changes in the Ventilation of Combusted Filtered Cigarettes

Background

The Behavioral and Clinical Pharmacology branch (BCP) previously authored a memo addressed to the Division of Product Science (DPS) outlining the changes in product characteristics that BCP reviews for SE Reports[1]. One of these characteristics is the ventilation of combusted filtered cigarettes. The January 23, 2018 memo stated that increases or decreases in ventilation of 20% or more from the predicate product to the new product would result in a BCP deficiency. This 20% change represented a *relative* change in ventilation between the new and predicate products. However, because ventilation data are expressed as a percentage, the approach provided in the January 23, 2018 memo creates limitations in review where either the new or predicate tobacco products are non-ventilated (i.e., 0% ventilation). A relative change cannot be calculated if the new product is ventilated and the predicate product is nonventilated (i.e., 0% ventilation), or vice versa. Therefore, BCP has revised its approach to reviewing SE Reports involving changes in the ventilation of combusted filtered cigarettes.

This memo thus amends the ventilation portion of the January 23, 2018 memo by providing a revised approach regarding the ventilation changes in SE Reports that will trigger a BCP deficiency. This memo also provides examples of deficiency language that can be included in SE reviews if a change in ventilation is substantial enough to trigger a BCP deficiency. This current BCP ventilation deficiency memo supersedes the ventilation information within the January 23, 2018 memo, which includes recommended deficiency language for ventilation deficiencies for ventilation changes of 20% or more between a new and predicate tobacco product.

[1] "BCP Reviews of Characteristic Changes in SE Reports," January 23, 2018

Scientific Rationale

The literature on combusted cigarettes indicates that reducing cigarette ventilation may result in increased delivery of HPHCs, including nicotine (Caraway et al., 2017; Ding, Trommel, Yan, Ashley, & Watson, 2005; Ding et al., 2006; Hammond et al., 2006; Kozlowski et al., 1998). However, increasing cigarette ventilation does not necessarily decrease harm. Some researchers have concluded that the introduction of filter ventilation in combusted cigarettes has contributed to a rise in the rate of lung adenocarcinomas in cigarette smokers (Song et al., 2017). In addition, the current literature on combusted cigarettes indicates that user behaviors change with the introduction of significant changes to ventilation (National Cancer Institute, 2001), such that smokers of ventilated cigarettes may engage in compensatory smoking by taking larger, more rapid, or more frequent puffs or blocking the ventilation holes with their lips or fingers (Creighton & Watts, 1972; Kozlowski, Frecker, Khouw, & Pope, 1980; Kozlowski & O'Connor, 2002; Kozlowski, Rickert, Pope, Robinson, & Frecker, 1982; Long, 1955; National Cancer Institute, 2001; Zacny, Stitzer, & Yingling, 1986). Further, ventilation allows ambient air to mix with the smoke before inhalation, which has the effect of lowering the smoke temperature and reducing the harshness of taste of the cigarette (Kozlowski & O'Connor, 2002). One industry study found that a change in ventilation from 0 to 12% significantly reduced “impact” and irritation of the mouth, nose, and throat (Hiriji & Hook, 1980), and another industry study found that an 8% increase in ventilation (from 25% to 33% ventilation) resulted in participants rating the more ventilated cigarette as milder and preferred (Philip Morris, 1989). This milder taste can result in a reduction of perceived health risk (Kozlowski & O'Connor, 2002). One study also showed that ventilated cigarettes are preferred over vent-blocked cigarettes (i.e., cigarettes that have been experimentally manipulated with blocked ventilation holes) when both types of cigarettes are available concurrently (Stein, Koffarnus, O'Connor, Hatsukami, & Bickel, 2018). In sum, decreasing ventilation may increase exposure to some HPHCs, and increasing ventilation may increase cigarette appeal and abuse liability. The best available evidence suggests an absolute change of 12% in ventilation is sufficient to impact measures of abuse liability. Therefore, an absolute change of 12% in ventilation from a predicate product to a new product may cause the new product to raise different questions of public health.

Product Change

Based upon our review of current literature and data:

If a new product has an *absolute* increase in ventilation of 12% or more from the predicate product to the new product, this change will likely result in a BCP deficiency.

Constituent yields from machine-generated smoking regimens (i.e., ISO and Canadian Intense) are needed to determine whether the new products raise different questions of public health. However, these data alone cannot be used to resolve an increased ventilation deficiency. Therefore, the BCP deficiency should recommend the applicant provide “information on biomarkers of exposure, use behaviors, or subjective effects for the new products and predicate products” in addition to ISO and Canadian Intense constituent yield data (see “Deficiency Language” below). Because such information is unlikely to be provided by the applicant in their first submission of an SE Report, the BCP deficiency can be inserted into a Deficiency letter during the first round of review. BCP will evaluate additional information provided by the applicant during subsequent rounds of review.

If a new product has an *absolute* decrease in ventilation of 12% or more from the predicate product to the new product, this change will likely result in a BCP deficiency.

This deficiency could be resolved through evaluation of constituent yield data from machine-generated smoking regimens (i.e., ISO and Canadian Intense). Such information might be provided by the applicant in their first submission of an SE Report. If ISO *and* Canadian Intense constituent yield data are not provided, the BCP deficiency can be inserted into a Deficiency letter during the first round of review, and BCP will evaluate additional information provided by the applicant in subsequent rounds of review. If ISO and Canadian Intense constituent yield data are provided in the first round, BCP will review the SE Report to determine whether a deficiency in warranted.

Example Deficiency Language

For absolute increases in ventilation of 12% or more, the following is an example of deficiency language that could be used in first round review. For other rounds of review revise the language to be responsive to the information submitted:

> SE00XXXXX, SE00XXXXX… provide information on changes to filter ventilation in the new products. The filter ventilation is substantially higher in these new products compared to the corresponding predicate products. Filter ventilation can affect exposure to nicotine and other HPHCs, as well as user behaviors and subjective effects of combusted cigarettes. For example, increasing filter ventilation may increase compensatory smoking behavior, such that smokers may take larger, more rapid, or more frequent puffs. In addition, increasing filter ventilation may reduce the harshness of combusted cigarette smoke, which may increase cigarette appeal and abuse liability. Provide scientific evidence and rationale to demonstrate that the filter ventilation increases do not alter exposure to nicotine or other HPHCs and do not cause the new products to raise different questions of public health. In addition to constituent yield data from ISO and Canadian Intense machine-generated smoking regimens, scientific evidence could include information on biomarkers of exposure, use behaviors, and subjective effects for the new and predicate products from a clinical study examining the effects of these products in appropriate populations. There could be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

For absolute decreases in ventilation of 12% or more, the following is an example of deficiency language that may be used:

> SE00XXXXX, SE00XXXXX… provide information on changes to filter ventilation in the new products. The filter ventilation is substantially lower in these new products compared to the corresponding predicate products. Filter ventilation can affect exposure to nicotine and other HPHCs. Provide scientific evidence and rationale to demonstrate that the filter ventilation decreases do not alter exposure to nicotine or other HPHCs and cause the new products to raise different questions of public health. Scientific evidence could include constituent yield data from ISO and Canadian Intense machine-generated smoking regimens. There could be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

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