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

Date: 9/30/19

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2019.10.04 14:07:14 -04'00'

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To: File

Subject: Behavioral and Clinical Pharmacology Guide for SE Reports

Behavioral and Clinical Pharmacology Reviewer Guide:
SE Reports

This document provides information that has been used to support **Behavioral and Clinical Pharmacology Branch** SE reviews. Note that this document is not intended to be an exhaustive catalogue of information relevant to review of an SE Report and reviewers are reminded that there may be more recent literature or studies that can be cited in support of your reviews. 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 specific 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, interested persons should not use this document as a tool, guide, or manual for the preparation of applications or submission to FDA.

A reviewer may use this document as a **general** guide for your review. Use the suggested deficiencies contained in this document to the extent that they are appropriate for the submission(s) you are reviewing. Additionally, you can use the text and/or references below as appropriate. **If you identify topics or references that should be added, please inform your Team Lead and/or Branch Chief.**

Press Control and click on any title in the Table of Contents to go directly to that page or use the Navigation Pane (under the View tab).

Table of Contents

COMBUSTED TOBACCO PRODUCTS

1. Nicotine yield or content in combusted products

Summary of the Literature

Nicotine is the primary addictive substance in tobacco products (e.g., U.S. Department of Health and Human Services, 1988). Changes in the amount and rate of nicotine delivered to the user will significantly impact the addictiveness of the product (e.g., Benowitz, Hukkanen, & Jacob, 2009). The amount of nicotine in a product has been shown to affect a user's nicotine exposure (e.g., Gross, Lee, & Stitzer, 1997; Pickworth, Fant, Nelson, Rohrer, & Henningfield, 1999).

Whereas machine-determined nicotine yields of cigarettes may be inadequate at estimating the population-level dose of nicotine in an individual smoker (Jarvis, Boreham, Primatesta, Feyerabend, & Bryant, 2001), within-subjects studies of cigarettes having different nicotine yields support a direct relationship between machine-smoked yield and nicotine exposure in individual smokers (Benowitz et al., 2012; Benowitz, Jacob, & Herrera, 2006). In a within-subject acute dosing study, Benowitz et al. (2006) found that systemic nicotine exposure varied linearly with both nicotine content of the cigarette and machine-determined nicotine yield (FTC mean nicotine yields = 0.13 to 0.96); moreover, systemic nicotine intake was greater than that predicted by the machine-determined yield. In a 6-month nicotine tapering study, Benowitz et al. (2012) found that progressively reducing nicotine content in cigarettes was associated with a progressive reduction in nicotine intake by participants. Reducing nicotine content of cigarettes reduces NNK; as nicotine content in cigarettes was reduced, machine-determined yields of NNK decreased, and participants showed decreased urinary NNAL (Benowitz et al., 2012). Mercincavage et al. (2016) also found that progressively reducing nicotine content in cigarettes was associated with a progressive reduction in urinary cotinine and NNAL levels. These studies suggest that nicotine yield does impact users' nicotine exposure. In addition, different nicotine yields were found to affect use behaviors and subjective effects ratings, which may further affect a product's abuse liability (Benowitz et al., 2006; Mercincavage et al., 2016).

Higher nicotine smoke yield may affect use behavior, increase nicotine exposure, and addiction (Benowitz et al., 2012; Benowitz et al., 2009; Benowitz et al., 2006). In contrast, reducing nicotine can result in changes in use behavior, including compensation (e.g., Benowitz et al., 2006) which may result in higher exposure to smoke constituents and HPHCs.

Example Deficiency Language

Missing Content/Yield

> **Example Deficiency:** SE000XXX, SE000XXX, ... do not provide information on nicotine yield in the new and predicate products. Nicotine is the primary addictive substance in tobacco products and changes in the amount and rate of nicotine delivered to the user will significantly impact the abuse liability of the product. Provide nicotine content and nicotine yield for the new and predicate products. If nicotine content/yields are different, provide scientific evidence demonstrating that the changes do not cause the new products to raise different questions of public health related to tobacco addiction, such as use behavior and pharmacokinetics.

Higher

> **Example Deficiency:** SE000XXX, SE000XXX, ... provide information on changes to nicotine content/smoke yield. The nicotine content/yield is higher in the new products compared with the corresponding predicate products. The higher nicotine content/yield may increase nicotine exposure and dependence, increase the abuse liability of the product, and alter user behaviors. Provide scientific evidence to demonstrate that the higher nicotine content/yield does not cause the new products to raise different questions of public health relating to tobacco addiction. Scientific evidence may include information on use behaviors or nicotine pharmacokinetics and constituent exposures for the predicate and new products.

Lower

> **Example Deficiency:** SE000XXX, SE000XXX, ... provide information on changes to nicotine content/smoke yield. The nicotine content/yield is lowered in the new products compared with the corresponding predicate products. The lowered nicotine content/yield may alter user behaviors (e.g., compensation and higher initiation). Provide scientific evidence to demonstrate that the lower nicotine content/yield does not cause the new products to raise different questions of public health relating to tobacco addiction. Scientific evidence may include information on use behaviors or nicotine pharmacokinetics and constituent exposures for the predicate and new products.

2. Ventilation/Draw Resistance (Filter Changes)

Summary of the Literature

The literature on combusted cigarettes indicates that user behaviors change with the introduction of changes to ventilation (e.g., National Cancer Institute, 2001). 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). Higher ventilation can result in lower resistance to draw, and a combusted cigarette with lowered resistance to draw requires less effort for smokers to increase their puff volume and smoke intake from the cigarette through larger, higher velocity puffs (e.g., Kozlowski & O'Connor, 2002; Zacny et al., 1986). One study showed that switching smokers to a cigarette with 30% reduced draw resistance was found to increase puff velocity and increase mouth nicotine intake (Dunn, 1978). Higher ventilation may also impact abuse liability by increasing free-base nicotine levels in mainstream smoke (e.g., Watson, Trommel, & Ashley, 2004). In addition, 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 (e.g., Kozlowski & O'Connor, 2002). One industry study found that increasing 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% higher 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). Another study also showed

that ventilated cigarettes are preferred over vent-blocked cigarettes (i.e., cigarettes that have been experimentally manipulated by blocking their ventilation holes) when both types of cigarettes are available concurrently (Stein, Koffarnus, O'Connor, Hatsukami, & Bickel, 2018). Preference for ventilated cigarettes is also apparent in the marketplace, as the majority of cigarette smokers in the US smoke ventilated (e.g., Centers for Disease Control and Prevention, 1998). In contrast to misperceptions that ventilated cigarettes are less harmful than nonventilated cigarettes, 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).

Reducing cigarette ventilation may result in higher delivery of HPHCs, including nicotine, should the user smoke the less ventilated product with the same intensity/topography as the predicate product (Caraway et al., 2017; Ding, Trommel, Yan, Ashley, & Watson, 2005; Ding et al., 2006; Hammond et al., 2006; Kozlowski et al., 1998). One industry study that analyzed data from multiple studies found that among a wide-range of cigarette brands tested, lowered ventilation was associated with higher exposure to nicotine and tar; however, there were exceptions where some higher-ventilated cigarettes were associated with higher nicotine and tar yields (Caraway et al., 2017). Another study analyzed cigarettes from three countries and found that cigarette ventilation was strongly associated with machine-smoked yields of tar, nicotine, and carbon monoxide (TNCO), wherein lowered ventilation was associated with higher TNCO (Kozlowski et al., 1998).

Product Change

Higher Ventilation

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, a BCP deficiency may recommend that 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).

Lower Ventilation

This deficiency could be resolved through evaluation of constituent yield data from machine-generated smoking regimens (i.e., ISO and Canadian Intense).

Example Deficiency Language

Higher Ventilation

Clinical data would aid in the evaluation of whether higher ventilation impacts user behavior or subjective effects for the new products. Clinical data, along with an evaluation of both ISO and Canadian Intense constituent yield data, may help in the determination of whether the new product raises different questions of public health.

> 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, higher filter ventilation may increase compensatory smoking behavior, such that smokers may take larger, more rapid, or more frequent puffs. In addition, higher 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 higher filter ventilation does 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.

Lower Ventilation

Evaluation of both ISO and Canadian Intense constituent yield data may aid in the evaluation of whether lower ventilation raises different questions of public health.

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 lower filter ventilation does 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.

3. Menthol (content/yield for combusted) - from non-menthol to menthol characterizing flavor

Summary of the Literature

The addition of menthol may increase the likelihood of initiation and progression to regular use, increase level/severity of dependence, and/or decrease likelihood of cessation success (e.g., Ahijevych & Garrett, 2010; Foulds, Hooper, Pletcher, & Okuyemi, 2010; Hersey, Nonnemaker, & Homsi, 2010; Hoffman & Miceli, 2011; Hoffman & Simmons, 2011; Kreslake, Wayne, & Connolly, 2008; Rock, Davis, Thorne, Asman, & Caraballo, 2010; Smith, Fiore, & Baker, 2014).

Youth and inexperienced smokers are more likely to experiment with and use menthol brands than non-menthol brands, therefore, these products may impact initiation behaviors and progression to regular smoking (e.g., Giovino et al., 2015; Hersey et al., 2006; Nonnemaker et al., 2013). Menthol may alter physiological responses to tobacco smoke, including attenuation of respiratory irritation from smoke constituents (e.g., acrolein, acetic acid, and cyclohexanone) (e.g., Ha et al., 2015; Willis, Liu, Ha, Jordt, & Morris, 2011) and reducing the perceived harshness of smoking (e.g., Buday et al., 2012; Pereira, Sim, Driver, Parker, & Fitzpatrick, 2013), thereby affecting smoking topography (e.g., Ahijevych & Garrett, 2004; Ahijevych & Parsley, 1999; Brinkman et al., 2012). Inhalation of menthol has been found to significantly decrease cough sensitivity in nonsmokers, supporting a chemosensory role in modulating respiratory irritation (Wise, Breslin, & Dalton, 2012).

Industry documents suggest that menthol reduces perceptions of harshness/irritation and increases sensation of airflow, which may increase inhalation depth and volume and thus exposure (Wayne & Connolly, 2004). A series of industry studies concluded that increasing or adding menthol and other flavors was associated with lowered perception of draw, which plays a role in topography (Kay & Morgan, 1994; Kreslake et al., 2008).

Studies suggest that menthol inhibits or slows nicotine metabolism and influences total metabolic clearance of nicotine (e.g., Benowitz, Herrera, & Jacob, 2004; Fagan et al., 2015; MacDougall, Fandrick, Zhang, Serafin, & Cashman, 2003; Muscat et al., 2009). Menthol and menthol derivatives may also increase membrane permeation to nicotine and NNN; one study found that 0.08% menthol increases the penetration of 3H-nicotine in ex vivo porcine oral mucosa (Squier, Mantz, & Wertz, 2010).

The addition of menthol may increase initiation and dependence, increase the product's novelty and palatability, produce sensory and physiological effects (e.g., cooling, analgesic effects) and alter user behaviors. Based on these findings, the addition of menthol to a non-mentholated product may cause the new product to raise different questions of public health regarding user behaviors and addiction.

Example Deficiency Language

> SE000XXX, SE000XXX, ... provide information on the menthol yield/content of the new and predicate products. The new products are mentholated whereas the predicate products are not. You claim that the addition of menthol does not cause the new products to raise different questions of public health. Mentholated tobacco products may impact initiation behaviors and progression to regular tobacco use by increasing palatability and reducing the likelihood of cessation in specific user populations. Provide scientific evidence to demonstrate that the changes in menthol do not cause the new products to raise different questions of public health. Scientific evidence may include information on use behaviors or nicotine pharmacokinetics and constituent exposures for the predicate and new products.

NONCOMBUSTED TOBACCO PRODUCTS

1. Free nicotine content/concentration in smokeless products

Summary of the Literature

Nicotine is the primary addictive constituent of tobacco products (e.g., Benowitz, 2010; Henningfield, Fant, & Tomar, 1997; Markou, 2008; U.S. Department of Health and Human Services, 1988; Watkins, Koob, & Markou, 2000). Like all drugs of abuse, the dose of nicotine is associated with its abuse liability. This is the case whether nicotine is administered alone (e.g., intravenously) or in a tobacco product (e.g., Henningfield, Miyasato, & Jasinski, 1985; Perkins et al., 1993).

Typically, empirical investigations of the abuse liability of nicotine or tobacco products compare nicotine doses or amounts that differ by 50% or more. Differences of this magnitude are strongly associated with differences in abuse liability outcomes (e.g., Henningfield et al., 1985; Higgins et al., 2017; Perkins et al., 1993). Evidence of dose-dependent effects of nicotine on abuse liability is robust (e.g., Henningfield et al., 1985; Higgins et al., 2017; Perkins et al., 1993). For example, the results of one recent study showed nicotine content predicted preference for cigarettes in an orderly, dose-dependent manner across several products that varied only in nicotine content (Higgins et al., 2017). Thus, higher and lower nicotine content produces reliable, dose-dependent changes in the abuse liability of tobacco products.

Exposure to nicotine from tobacco products, including smokeless tobacco (ST), is dependent on a variety of factors. For example, one study found ST use topography (e.g., duration of use) is associated with nicotine exposure (Hatsukami, Keenan, & Anton, 1988). Another study found consuming coffee and cola may reduce nicotine absorption from nicotine gum by acidifying salivary pH (Henningfield, Radzius, Cooper, & Clayton, 1990) —a finding that could generalize to ST use. In addition, characteristics of ST products, including nicotine content, can affect nicotine exposure (e.g., Digard, Proctor, Kulasekaran, Malmqvist, & Richter, 2012). Moreover, considerable evidence suggests changes in the free nicotine content of ST products independently affects nicotine exposure and abuse liability.

Nicotine occurs in several chemical states, including bound to hydrogen ions (i.e., mono-protonated and diprotonated nicotine) and unbound (i.e., unprotonated, unionized, or free nicotine). The amount of free nicotine contained in an ST product is determined by total nicotine content and the pH of the product (Henningfield, Radzius, & Cone, 1995). Free nicotine content affects nicotine exposure because free nicotine more readily crosses biological membranes, including oral mucosa (e.g., L. H. Chen, Chetty, & Chien, 1999; Nair, Chetty, Ho, & Chien, 1997; Nielsen & Rassing, 2002). Free nicotine varies widely in smokeless tobacco products (Henningfield et al., 1995).

Results from clinical studies conducted under well-controlled laboratory conditions suggest free nicotine content affects ST abuse liability. For example, Fant and colleagues examined the effects of multiple ST products on nicotine pharmacokinetics and pharmacodynamics in current users (Fant, Henningfield, Nelson, & Pickworth, 1999). The ST products used in the study were commercially available moist snuff tobacco products (Copenhagen, Skoal Long Cut Cherry, Skoal Original Wintergreen, and Skoal Bandits) that were chosen based on differences in free nicotine content. The researchers found positive relations between free nicotine content and several outcomes, including plasma nicotine concentration, heart rate, and subjective effects. One limitation of this study was that the effects of free nicotine content on

study outcomes were not isolated because other characteristics (i.e., flavorings, binders, sweeteners, etc.) varied between products. Nevertheless, data from this study show orderly associations between free nicotine content and various measures of abuse liability.

Pickworth and colleagues also examined the effects of ST pH on nicotine absorption (Pickworth, Rosenberry, Gold, & Koszowski, 2014). The researchers used a referent unflavored moist snuff tobacco product obtained from a university tobacco program. All product characteristics (e.g., water content, tobacco blend, and nicotine content) were held constant across experimental products except pH and methyl salicylate (an ingredient used in wintergreen flavoring). The researchers manufactured three products: 1) ST with pH 5.4 (< 0.5% free nicotine) and methyl salicylate, 2) ST with pH 7.7 (32% free nicotine) and no methyl salicylate, and 3) ST with pH 8.3 (66% free nicotine) and methyl salicylate. Participants were exposed to all three products in separate experimental sessions. Plasma nicotine concentration was higher following administration of the two ST products with higher pH relative to the product with lower pH. In addition, the rate of nicotine absorption was much faster in the products with higher pH levels. Notably, no differences in plasma nicotine concentration were observed between the two products with the highest pH levels. However, study limitations (e.g., differences in methyl salicylate content between these two products) may have contributed to this finding. Nevertheless, the study found large differences in plasma nicotine in the product with the lowest pH relative to the product with the highest pH, and both products had the same methyl salicylate content. The researchers concluded, "these results indicate that pH is a primary determinant of buccal nicotine absorption."

Surveillance and monitoring studies of commercially available ST products have shown that pH levels vary widely between products, resulting in percentages of free nicotine in ST products that range from less than 1% to over 75% (e.g., Richter, Hodge, Stanfill, Zhang, & Watson, 2008). Such differences in the free nicotine content of ST products can impact abuse liability in various ways. For example, evidence from survey studies and industry documents suggests "starter" ST products with low free nicotine content are marketed to inexperienced users (e.g., Connolly, 1995; DPG Claessens Product-Consultants BV, 1981; Tomar, Giovino, & Eriksen, 1995). Thus, lowering the free nicotine content of ST may increase initiation. Evidence also suggests consumers who begin ST use with starter products are likely to "graduate" to products with higher free nicotine content—products that are associated with higher use and greater signs of dependence (Connolly et al., 1986; Tomar et al., 1995). Thus, higher free nicotine content in ST may increase dependence.

In sum, evidence suggests higher free nicotine content of ST results in larger, more rapid increases in plasma nicotine (e.g., Fant et al., 1999; Pickworth et al., 2014). These effects occur independent of use topography (e.g., duration of use) and other use behaviors (e.g., consuming coffee and cola) when these behaviors are controlled under laboratory conditions. Additional evidence suggests lowering free nicotine may increase the likelihood of ST initiation and higher free nicotine may increase the likelihood of dependence (Tomar et al., 1995).

To calculate free nicotine:

pH = pKa + log (free NIC/(total NIC – free NIC))
Rearranging this equation and inserting pKa = 8.02
$10^{pH-8.02}$ = free NIC/(total NIC – free NIC)
Solving for free NIC
Free (NIC) = ([$10^{pH-8.02}$] total NIC) / (1 + [$10^{pH-8.02}$])

Note: Do not use [total NIC] for [BH+] in HH equation. [BH+] = [total NIC] – [free NIC].

Example Deficiency Language:

Higher

> **Example Deficiency:** SE000XXX, SE000XXX, ... provide information on changes to free nicotine content/concentration. The free nicotine content/concentration is higher in the new products compared with the corresponding predicate products. The higher free nicotine content/concentration may increase nicotine exposure and dependence, increase the abuse liability of the product, alter user behaviors, and may increase NNN exposure. Provide scientific evidence to demonstrate that the changes in free nicotine content/concentration do not cause the new products to raise different questions of public health relating to tobacco addiction. Scientific evidence may include information on use behaviors or nicotine pharmacokinetics and constituent exposures for the predicate and new products.

Lowered

> **Example Deficiency:** SE000XXX, SE000XXX, ... provide information on changes to free nicotine content/concentration. The free nicotine content/concentration is lowered in the new products compared with the corresponding predicate products. Lowered free nicotine content/concentration may alter user behaviors (e.g., compensation and initiation). Provide scientific evidence to demonstrate that the changes in free nicotine content/concentration do not cause the new products to raise different questions of public health relating to tobacco addiction. Scientific evidence may include information on use behaviors or nicotine pharmacokinetics and constituent exposures for the predicate and new products.

2. Menthol (content for smokeless) - from non-menthol to menthol characterizing flavor

Summary of the Literature

Flavoring in tobacco has been found to attract youth and new users (e.g., Delnevo et al., 2014; Minaker, Ahmed, Hammond, & Manske, 2014; Oliver, Jensen, Vogel, Anderson, & Hatsukami, 2013). Menthol may attenuate the aversive effects of nicotine (e.g., Fan et al., 2016), and it has been used by manufacturers to improve the palatability of tobacco products (e.g., Carpenter, Wayne, Pauly, Koh, & Connolly, 2005; Minaker et al., 2014). The addition of menthol may also impact nicotine absorption as menthol has been

shown to increase the permeability of membranes and the penetration of nicotine across the oral mucosa in vitro (e.g., Squier et al., 2010), although in vivo data are lacking.

Levels of menthol similar to or in excess of those added to confectionary products that use menthol as a flavor may be discernable to the consumer (C. Chen, Isabelle, Pickworth, & Pankow, 2010). In a report on levels of mint and wintergreen flavors in smokeless tobacco and confectionary products an average of 3.5 mg/g was found for the most five most-highly mentholated confectionery products and 2.1mg/g for mentholated hard candy. In comparison, of the ST products analyzed, the highest menthol level was 5.3 mg/g and an average of the five most mentholated ST products was 4.3 mg/g (C. Chen et al., 2010).

Example Deficiency Language:

> SE000XXX, SE000XXX, ... provide information on the menthol yield/content of the new and predicate products. The new products are mentholated whereas the predicate products are not. You claim that the addition of menthol does not cause the new products to raise different questions of public health. Mentholated tobacco products may impact initiation behaviors and progression to regular tobacco use by increasing palatability and reducing the likelihood of cessation in specific user populations. Provide scientific evidence to demonstrate that the changes in menthol do not cause the new products to raise different questions of public health. Scientific evidence may include information on use behaviors or nicotine pharmacokinetics and constituent exposures for the predicate and new products.

3. Flavors in smokeless tobacco - from tobacco (non-flavored) to flavored characterizing flavor

Summary of the Literature

Smokeless products with strong non-tobacco flavors are primarily used by inexperienced users who often initiate smokeless tobacco use with flavored products (e.g., Alpert, Koh, & Connolly, 2008; Connolly, 1995; Djordjevic, Hoffmann, Glynn, & Connolly, 1995; Harris, Stepanov, Pentel, & Lesage, 2012; Henningfield et al., 1995; Oliver et al., 2013) and therefore, these flavor changes may cause the new products to impact initiation, tobacco addiction, and continued use (e.g., Henningfield, Hatsukami, Zeller, & Peters, 2011; Oliver et al., 2013; Stanfill et al., 2011; Villanti, Richardson, Vallone, & Rath, 2013). Flavored smokeless tobacco products may act as starter product to the inexperienced user and impact initiation behaviors and progression to tobacco addiction since palatability influences abuse liability (e.g., Carter et al., 2009; Henningfield et al., 2011). Change in flavors may cause the new products to raise different questions of public health due to changes in product attractiveness, tobacco addiction, and user behavior.

Example Deficiency Language:

> SE000XXX, SE000XXX, ... provide information on the addition of a characterizing flavor of XXXX to the new product while the predicate product does not have a characterizing flavor. You claim that the addition of a characterizing flavor does not cause the new product to raise different questions of public health. Changes in flavor may affect use behaviors, such as deposition time in the mouth (e.g., use topography) and cause the new product to impact initiation and use behaviors. Provide scientific evidence to demonstrate that the characterizing flavor does not

cause the new product to raise different questions of public health. Scientific evidence may include information on use behaviors or nicotine pharmacokinetics and constituent exposures for the predicate and new products.

Notes/Definitions

1. Puffing topography refers to an individual's per-cigarette puffing profile which consists of number of puffs, puff volume, puff duration, puff velocity, and inter-puff interval
2. Other smoking behaviors can include the number and timing of cigarettes smoked per day, the length of cigarette smoked, and blocking of ventilation holes
3. Ventilation is sometimes referred to as dilution (air dilution of smoke). We use 'ventilation' in the SE review
4. Draw resistance is sometimes referred to as "resistance to draw" or "draft holes open," we use 'draw resistance' in the SE review

Surrogates

Example language for when the applicant includes information about a surrogate, but a surrogate is not needed:

> The applicant supplied information in amendment XXXX about the XXXX content in a surrogate for the predicate product. The applicant has supplied data from a surrogate new product in response to this deficiency. Addiction defers to Chemistry for the determination of the acceptability of surrogate products. In this case, Chemistry has found that the extrapolation of the data from the surrogate new product to the new product is not needed, because the applicant has provided the data for both the new and predicate products in the original applications. They have also provided the estimation of the XXXX content in the new products and predicate product in the response to this deficiency. Therefore, because data has been provided for the new and predicate products, evaluation regarding the appropriateness of the chemistry data extrapolation from the surrogate new product to the new product is not needed.

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