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.

FDA U.S. FOOD & DRUG ADMINISTRATION

Memorandum

To: Division of Product Science and to File

From: Chad Reissig, Ph.D.
Branch Chief, Behavioral and Clinical Pharmacology
Office of Science, CTP

Digitally signed by Chad Reissig -S
Date: 2018.03.05 13:14:14 -05'00'

Through: Iilun Murphy, M.D.
Director, Division of Individual Health Science
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Iilun C. Murphy -S
2018.03.05 14:01:00 -05'00'

Subject: BCP Reviews of Characteristic Changes in SE Reports

This memo outlines product characteristic changes that the Behavioral and Clinical Pharmacology (BCP) Branch currently reviews for SE reports. Additional issues determined relevant by the TPL may also be sent to our branch for review. The purpose of this memo is to communicate to the TPL the areas that BCP recommends inclusion for review assignment and to provide boilerplate deficiency language for the first-round review cycle. This may help avoid situations in which BCP is requested to complete a full SE review after the start of the review without a deadline extension.

BCP requests to be involved from the earliest round of SE report review as possible to avoid the introduction of novel deficiencies in subsequent rounds of review. Given the brevity of data typically provided in applications submitted to the SE pathway, BCP has provided stock deficiency language concerning product characteristic changes that should receive BCP input. This language can be inserted into a TPL memo or other discipline review in the first round of reviews, allowing for appropriate BCP input and review in subsequent rounds.

This list of characteristics described below may evolve with advances in tobacco regulatory science.

The following changes in characteristics and related stock deficiency language are as follows:

1. Nicotine yield or content in combusted products (if content values are within ±20%, yield data do not raise a deficiency)
    i. Increase from predicate product to new product of 20% or more
        - **Deficiency**: SE000XXX, SE000XXX, … provide information on changes to nicotine content/smoke yield. The nicotine content/yield is increased in the new products compared with the corresponding predicate products. The increased 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 increase in 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. There may be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

ii. Decrease from predicate product to new product of 20% or more

- **Deficiency**: SE000XXX, SE000XXX, … provide information on changes to nicotine content/smoke yield. The nicotine content/yield is decreased in the new products compared with the corresponding predicate products. The decreased nicotine content/yield may alter user behaviors (e.g., compensation and increased initiation). Provide scientific evidence to demonstrate that the decrease in 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. There may be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

2. Free nicotine content/concentration in smokeless products (depending on what data are reported by the Applicant)

i. Increase from predicate product to new product of 20% or more

- **Deficiency**: SE000XXX, SE000XXX, … provide information on changes to free nicotine content/concentration. The free nicotine content/concentration is increased in the new products compared with the corresponding predicate products. The increased 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. There may be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

ii. Decrease from predicate product to new product of 20% or more

- **Deficiency**: SE000XXX, SE000XXX, … provide information on changes to free nicotine content/concentration. The free nicotine content/concentration is decreased in the new products compared with the corresponding predicate products. Decreased 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. There may be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

3. Ventilation

i. Increase from predicate product to new product of 20% or more

- **Deficiency:** SE000XXX, SE000XXX, … provide information on changes to filter ventilation in the new products. Filter ventilation is increased in the new products relative to the predicate products. Filter ventilation can affect user behaviors as well as nicotine pharmacokinetics. Provide scientific evidence to demonstrate that the changes in filter ventilation 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. There may be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

ii. Decrease from predicate product to new product of 20% change or more

- **Deficiency:** SE000XXX, SE000XXX, … provide information on changes to filter ventilation in the new products. Filter ventilation is decreased in the new products compared to the predicate products. Filter ventilation can affect user behaviors as well as nicotine pharmacokinetics. Provide scientific evidence to demonstrate that the changes in filter ventilation 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. There may be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

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

- **Deficiency:** 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. There may be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

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

- **Deficiency:** 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. There may be other ways of satisfying this deficiency and you are responsible for identifying how best to do this

6. Changes in tube length, diameter length (often engineering is the primary deficiency) 20%
    - **Deficiency**: SE000XXX, SE000XXX, … provide information on changes in length/diameter between the new and corresponding predicate products. Changes in physical dimensions of the new products may affect the abuse liability, use behaviors, and the toxicant exposure profile of the new products compared to the corresponding predicate products. One way to address this deficiency would be to provide clinical data to support your assertion that the differences in length/diameter 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. There may be other ways of satisfying this deficiency and you are responsible for identifying how best to do this.

7. Novel format changes (e.g. to a dissolvable, but NOT to include loose vs. portioned ST changes) – defer to TPL