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.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Tobacco Products
Silver Spring, MD 20993

MEMORANDUM

From: Matthew R. Holman, Ph.D.
Director, Division of Product Science
Office of Science

Digitally signed by Matthew R. Holman -S
Date: 2016.09.19 11:42:51 -04'00'

Through: Cristi Stark, M.S.
Associate Director, Science Policy
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Date: 2016.09.19 15:58:42 -04'00'

To: Walter Ellenberg, Ph.D.
Director, Division of Regulatory Health Project Management
Office of Science

Subject: Use of Surrogate Tobacco Products in SE Reports[1]

Background

Food and Drug Administration (FDA) has advised manufacturers that they may be able to submit information and data for surrogate tobacco products in SE Reports if they are not able to provide all information and data for the new and predicate tobacco products necessary to demonstrate substantial equivalence. As a consequence, numerous SE Reports that have begun scientific review over the past few years have included information and data for surrogate tobacco products. However, there appears to be considerable variability in how applicants rely on surrogate tobacco products, as the information and data submitted for surrogate tobacco products varies significantly among different SE Reports. Therefore, this memorandum seeks to clarify how FDA defines predicate tobacco products and surrogate tobacco products along with examples of how surrogate tobacco products may be effectively used in an SE Report to support a determination of substantial equivalence.

[1] On March 10, 2016, FDA issued a memo on this topic. This current memo corrects a typographical error regarding whether surrogate tobacco products need to be uniquely identified. This current memo supersedes the March 10, 2016, memo.

Discussion

An eligible predicate tobacco product for a SE Report is *either* one of the following:

1. A product that was commercially marketed in the United States (other than in test markets) as of February 15, 2007
2. A product that was previously found to be substantially equivalent by FDA

The determination for a finding of substantial equivalence is made by comparing a new tobacco product to a predicate tobacco product. If multiple predicate tobacco products are identified in an SE Report, the substantial equivalence determination is based on the comparison of the new tobacco product to each individual predicate tobacco product.

A surrogate is a tobacco product for which an applicant provides data it would like to extrapolate to the new, predicate tobacco product or both new and predicate tobacco products. However, the surrogate tobacco product is neither the new or predicate tobacco product. Data for a surrogate tobacco product is provided in place of data or to provide a bridge between data for the new or predicate tobacco product. A surrogate tobacco product is used when there is inadequate data available for the new or predicate tobacco product; data for a surrogate tobacco product supplement the data for a new or predicate tobacco product. Unlike predicate tobacco products, surrogate tobacco product data may be in place at the start of substantive scientific review or may be provided in response to a deficiency letter. In order to adequately evaluate a surrogate tobacco product data, the following information must be provided by the applicant:

- List of characteristics for the surrogate tobacco product in order to determine whether the data generated from the surrogate tobacco product can be extrapolated to the new or predicate tobacco product.

- An explanation of why data from the surrogate tobacco product can be extrapolated to the new or predicate tobacco product and how the surrogate tobacco product provides evidence that differences in characteristics between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.

Grandfathered determination is not necessary for a surrogate tobacco product, as it is not a predicate tobacco product.

To understand how surrogate tobacco products are used, consider the following example. An SE Report for a pouched moist snuff may include free nicotine data for a tobacco product that serves as a surrogate for the predicate tobacco product because the applicant no longer manufactures the predicate tobacco product but manufactures the surrogate tobacco product and, therefore, can analyze it for free nicotine. In this example, the SE Report may include blend information for the predicate and surrogate tobacco products demonstrating that the

products have nearly identical blends (i.e., no significant differences in tobacco and additives in the filler). The applicant could indicate that, because of the nearly identical blends, free nicotine data for the surrogate tobacco product can be extrapolated to the predicate tobacco product.

Another example would be an SE Report with a new tobacco product that is a king-size cigarette for which the applicant does not have TSNA data but the applicant does have TSNA data for a surrogate tobacco product. In this example, the surrogate tobacco product could be identical to the new tobacco product except that it is a 100 mm cigarette. The applicant could submit TSNA filler data for the surrogate tobacco product and assert that the TSNAs quantities in the surrogate product filler are the same as those in the new product filler.

In addition to new, predicate, and surrogate tobacco products, SE Reports sometimes contain information and data for other marketed tobacco products. Data for these other marketed products may be provided after the start of substantive scientific review and in response to a deficiency letter. These products are not surrogate tobacco products for the following reasons:

- A full comparison of the characteristics for other marketed products and the new or predicate tobacco product are not provided.

- The applicant does not extrapolate data from these products to the new or predicate products. Instead, applicants use these products to provide some characteristics of tobacco products on the market in an effort to demonstrate that the new and predicate tobacco products are similar in characteristics to other marketed tobacco products.

Because these products are not new, predicate, or surrogate tobacco products, the following information is not required:

- Unique identification is not required for other marketed tobacco products.

- Grandfathered determination is not necessary for other marketed tobacco products.

In general, FDA does not believe data from other marketed tobacco product are useful in a substantial equivalence application. To understand how other marketed tobacco products have been used by applicants, consider the following example. HPHC testing of the new and predicate tobacco products may have shown significant increases in carbon monoxide and BaP yields from the new tobacco product relative to yields from the predicate tobacco product. The applicant may provide carbon monoxide and BaP yields from other marketed products to argue that, even though carbon monoxide and BaP yields increased in the new tobacco product, the new tobacco product does not raise different questions of public health because the yields are similar to other marketed tobacco products. Information and data such as this for other marketed tobacco products does not support a finding of substantial equivalence because it does not demonstrate the public health impact of the differences in characteristics between

the new and predicate tobacco products; it provides evidence about the public health impact of the new tobacco product compared to other marketed tobacco products.

Although this memorandum explains the statutory definition of a predicate tobacco product and how FDA defines both a surrogate tobacco product and other marketed tobacco products used in an SE Report, applicants do not always define predicate and surrogate tobacco products as described in this memorandum. SE Reports often include tobacco products identified using terms such as "SE comparison product." Because of the ambiguity in terms that applicants use to identify tobacco products, it is sometimes difficult for FDA to clearly understand the applicant's intended use of such products in demonstrating substantial equivalence. Therefore, in SE Reports where an applicant is not clear on the type of product provided (e.g., surrogate, predicate or other), FDA should seek clarification from applicants regarding whether a given tobacco product is a predicate tobacco product, surrogate tobacco product, or some other marketed tobacco product included to provide supplemental information on marketed tobacco products. It is important that FDA clearly understands the applicant's intent in order to appropriately evaluate the SE Report.

Recommendation

If an SE Report identifies more than one product as a predicate tobacco product, FDA should base the substantial equivalence determination on the comparison of the new tobacco product to each individual predicate tobacco product. Each predicate tobacco product must be uniquely identified and must be demonstrated to be an eligible predicate tobacco product. However, in such SE Reports, if an applicant identifies a product as a "predicate product" or a "comparator product" and it is unclear based on the data provided that the applicant truly intends the product to be a predicate tobacco product, then FDA should seek clarification from the applicant. Clarification should be sought if limited information and data is provided for product identified as a "predicate product," as this suggests that the applicant may intend the product to be a surrogate tobacco product. For such SE Reports, RHPMs should convey the following language to the applicant[2]:

> Your SE Report includes information and data for [INSERT PRODUCT NAME], but it is unclear whether this product is predicate or surrogate tobacco product. Predicate and surrogate tobacco products differ as follows:
>
> - An eligible predicate tobacco product for a SE Report is *either* one of the following:
>   - A product that was commercially marketed in the United States (other than in test markets) as of February 15, 2007

[2] The applicant is required to submit an amendment through the CTP DCC to include their clarification in the administrative record. If a phone request is placed for clarification, FDA should receive the amendment within one week (7 calendar days). If the amendment is not received within one week, the deficiency will be communicated via letter.

    - A product that was previously found to be substantially equivalent by FDA
- A surrogate is a tobacco product for which an applicant provides data it would like to extrapolate to the new, predicate tobacco product or both the new and predicate tobacco products. However, the surrogate tobacco product is neither the new or predicate tobacco product.

Clarify whether [INSERT PRODUCT NAME] is a predicate or surrogate tobacco product.

If the tobacco product is a predicate tobacco product, provide *all* of the following information or indicate where it is provided in your SE Report:

a. Properties sufficient to uniquely identify the predicate tobacco product
b. Evidence demonstrating that the product is predicate eligible (meaning grandfathered or previously found substantially equivalent)
c. Comparison of the characteristics of new and predicate tobacco products to demonstrate that any differences in characteristics do not cause the new tobacco product to raise different questions of public health

If the tobacco product is a surrogate tobacco product, provide *all* of the following information or indicate where it is provided in your SE Report:

d. Sufficient characteristics of the surrogate tobacco product in order to compare it to the new or predicate tobacco product and determine whether extrapolation of data from the surrogate tobacco product to the new or predicate tobacco product is appropriate
e. An explanation for why data from the surrogate tobacco product can be extrapolated to the new or predicate tobacco product and how the surrogate tobacco product provides evidence that differences in characteristics between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health