Appendix

Information to Consider for Smokeless Tobacco Products

The information included in this appendix reflects deficiencies frequently seen in previous SE Reports for smokeless tobacco products that FDA has reviewed. It should be noted that, although this information is specific to smokeless tobacco products, some of it may not be applicable to your SE Report. If a difference exists between the new and predicate tobacco products, provide a rationale for each difference with scientific evidence and a discussion for why the difference does not cause the new tobacco product to raise different questions of public health. To the extent that it is applicable, you can use this information to determine whether your SE Report should be amended prior to FDA's review of your SE Report.

Identification of the New and Predicate Tobacco Products

Unique identification is an important element for new and predicate tobacco products. Unique identification is necessary so that FDA can accurately identify which products should be compared for a determination of substantial equivalence. Without unique identification, it is difficult for FDA to begin a scientific comparison to determine substantial equivalence.

Unique identification may include, but is not limited to, attributes such as brand, name, descriptors, packaging, size, count, and unit of use. You should provide the following information to uniquely identify the new **and** predicate tobacco products:

- The manufacturer
- Product name, including the brand and subbrand
- Product category, product subcategory, and product properties, as provided in Table 1

Table 1. Smokeless Subcategory and Corresponding Product Properties

Smokeless Subcategory	Product Properties
Loose Moist Snuff	• Package type (e.g., plastic can with metal lid, plastic can with plastic lid) • Package quantity (e.g., 20 grams (g), 2 ounces) • Tobacco cut size (e.g., 5 mm, 7 mm) • Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) • Additional properties needed to uniquely identify the tobacco product (if applicable)
Portioned Moist Snuff	• Package type (e.g., plastic can with metal lid, plastic can with plastic lid) • Package quantity (e.g., 22.5 g, 20 g) • Portion count (e.g., 15 pouches, 20 pieces) • Portion mass (e.g., 1.5 g/pouch, 2 g/piece) • Portion length (e.g., 15 mm, 20 mm) • Portion width (e.g., 10 mm, 15 mm) • Portion thickness (e.g., 5 mm, 7 mm) • Tobacco cut size (e.g., 5 mm, 7 mm) • Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) • Additional properties needed to uniquely identify the tobacco product (if applicable)
Loose Snus	• Package type (e.g., plastic can with metal lid, plastic can with plastic lid) • Package quantity (e.g., 20 g, 2 ounces) • Tobacco cut size (e.g., 5 mm, 7 mm) • Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) • Additional properties needed to uniquely identify the tobacco product (if applicable)
Portioned Snus	• Package type (e.g., plastic can with metal lid, plastic can with plastic lid) • Package quantity (e.g., 22.5 g, 20 g) • Portion count (e.g., 15 pouches, 20 pieces) • Portion mass (e.g., 1.5 g/pouch, 2 g/piece) • Portion length (e.g., 15 mm, 20 mm) • Portion width (e.g., 10 mm, 15 mm) • Portion thickness (e.g., 5 mm, 7 mm) • Tobacco cut size (e.g., 5 mm, 7 mm) • Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) • Additional properties needed to uniquely identify the tobacco product (if applicable)
Loose Dry Snuff	• Package type (e.g., plastic can with metal lid, plastic can with plastic lid) • Package quantity (e.g., 20 g, 2 ounces) • Tobacco cut size (e.g., 0.05 mm, 0.07 mm) • Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) • Additional properties needed to uniquely identify the tobacco product (if applicable)

Dissolvable	• Package type (e.g., plastic can with metal lid, plastic can with plastic lid) • Package quantity (e.g., 22.5 g, 20 g) • Portion count (e.g., 15 sticks, 20 tablets) • Portion mass (e.g., 1.5 g/strip, 1.0 g/piece) • Portion length (e.g., 10 mm, 15 mm) • Portion width (e.g., 5 mm, 8 mm) • Portion thickness (e.g., 3 mm, 4 mm) • Tobacco cut size (e.g., 0.05 mm, 0.07 mm) • Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) • Additional properties needed to uniquely identify the tobacco product (if applicable)
Loose Chewing Tobacco	• Package type (e.g., bag, pouch, wrapped) • Package quantity (e.g., 20 g, 3 ounces) • Tobacco cut size (e.g., 0.05 mm, 0.07 mm) • Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) • Additional properties needed to uniquely identify the tobacco product (if applicable)
Portioned Chewing Tobacco	• Package type (e.g., plastic can with metal lid, plastic can with plastic lid) • Package quantity (e.g., 20 g) • Portion count (e.g., 10 bits) • Portion mass (e.g., 2 g/bit) • Portion length (e.g., 8 mm, 10 mm) • Portion width (e.g., 6 mm, 8 mm) • Portion thickness (e.g., 5 mm, 7 mm) • Characterizing flavor(s) (e.g., none, menthol, cherry, wintergreen) • Additional properties needed to uniquely identify the tobacco product (if applicable)
Smokeless Co-Package	• For a new co-packaged tobacco product composed of multiple smokeless tobacco products, include all properties for each individual tobacco product as identified above
Other	• Package type (e.g., bag, box) • Package quantity • Characterizing flavor(s) (e.g., none, tobacco, menthol) • Additional properties needed to uniquely identify the tobacco product

Clarification of Names for New and Predicate Tobacco Products

When identifying a new or predicate tobacco product using a different name than previously used in the SE Report or used in other submissions (e.g., a standalone grandfather submission), it is important to identify whether the characteristics are identical to the tobacco product with the previous name or have been modified. If the characteristics are identical, you should include a statement to this effect within the SE Report (e.g., "_____" had a name change to "_____" and all characteristics are identical; the only difference is the product name). If the characteristics are not identical, each difference should be described. You may also list all the names (aliases) that are used to identify the same tobacco product (e.g., Tobacco Product A is also named Tobacco Product X and Z and all tobacco products are manufactured with the same characteristics). It is important to note that, if the characteristics of the tobacco product have been modified during the application review process (e.g., within an SE Report amendment), the modified product will not be reviewed, as it is considered a different tobacco product and requires a separate application.

Evidence of an Eligible Predicate Tobacco Product

An eligible predicate tobacco product is either a grandfathered tobacco product (i.e., commercially marketed in the United States other than exclusively in test markets as of February 15, 2007) or a tobacco product previously found substantially equivalent by FDA.

If you select a predicate tobacco product that is grandfathered, you may reference the submission tracking number (STN) and product name of the standalone grandfather submission if one exists. Alternatively, you can provide specific information sufficient to support a grandfathered determination:

1. Identification of the predicate tobacco product, including but not limited to the name, category, subcategory, package type, package quantity, characterizing flavor, and other additional properties necessary to uniquely identify the product (e.g., length, diameter, and ventilation for combusted, filtered cigarettes)

2. Adequate information to demonstrate that the tobacco product was commercially marketed (other than exclusively in test markets) in the United States as of February 15, 2007. FDA interprets "as of" to mean "on." If you cannot provide documentation that the tobacco product was specifically commercially marketed *on* February 15, 2007, FDA suggests that you provide documentation of commercial marketing for a reasonable period of time before and after February 15, 2007. Examples of such information may include, but are not limited to:

    - Dated copies of advertisements
    - Dated catalog pages
    - Dated promotional material
    - Dated trade publications
    - Dated bills of lading
    - Dated freight bills
    - Dated waybills
    - Dated invoices
    - Dated purchase orders
    - Dated customer receipts
    - Dated manufacturing documents
    - Dated distributor or retailer inventory lists
    - Any other document you believe demonstrates that the tobacco product was commercially marketed (other than exclusively in test markets) in the United States as of February 15, 2007

    If applicable, you should include a brief statement identifying and explaining all citations and abbreviations (e.g., item number and/or product description) used in the documentation that reference the predicate tobacco product.

3. A statement that the predicate tobacco product was not exclusively in a test market as of February 15, 2007.

4. A brief description of how the predicate tobacco product is used by the consumer.

If you select a predicate tobacco product that was previously found substantially equivalent, provide the STN and predicate tobacco product name used within that submission (i.e., SE Report where the new tobacco product was found to be substantially equivalent).

Use of a Predicate Tobacco Product You No Longer Manufacture

If you no longer manufacture the predicate tobacco product, you should still fully characterize the predicate tobacco product in order for FDA to determine all differences in characteristics between the new and predicate tobacco products. Data on the predicate tobacco product may be required to demonstrate substantial equivalence of the new tobacco product. Some potential options for obtaining data on the predicate tobacco product include:

1. Manufacture the predicate tobacco product at present day, consistent with the product composition and design specifications in place at the time the predicate tobacco product was originally manufactured. In this case, design parameter data should be accompanied by documentation demonstrating that the manufacture of the predicate tobacco product at present day is reflective of the predicate tobacco product at the time of original manufacture. Where any difference exists between the present-day predicate tobacco product design parameters, components, or constituents and the original predicate tobacco product, those differences should be noted, and the present-day predicate tobacco product will be considered a surrogate tobacco product (see "Use of a Surrogate Tobacco Product" below).

2. Identify another, currently available tobacco product with design parameters, components, and constituents similar to the predicate tobacco product. This tobacco product will be considered a surrogate tobacco product (see "Use of a Surrogate Tobacco Product" below). Where any difference exists between the surrogate tobacco product design parameters, components, or constituents and the predicate tobacco product, those differences should be noted.

Use of a Predicate Tobacco Product that You Do Not Own

If you do not own the predicate tobacco product, you should still provide full characterization of the predicate tobacco product. Without this information, FDA cannot determine what all of the differences in characteristics of the new and predicate tobacco products are. For example, see "Adequate Tobacco and Ingredient Information" below. An explanation of the means by which you obtained the supplied information and certification that you have access to the product composition information for the predicate tobacco product from the manufacturer is necessary.

Use of a Surrogate Tobacco Product

A predicate tobacco product must have been commercially marketed in the United States (other than exclusively in test markets) as of February 15, 2007, or previously found to be substantially equivalent by FDA. A new tobacco product must be compared to a predicate tobacco product for FDA to determine whether the new tobacco product is substantially equivalent; all SE orders issued by FDA are based on a comparison of the new tobacco product to a predicate tobacco product.

In some cases, however, an applicant may use a surrogate tobacco product (a tobacco product that is neither the new or predicate tobacco product) to provide test data (e.g., harmful and potentially harmful constituents [HPHC] test data). Data for the surrogate tobacco product are provided *in place of* data for the new or predicate tobacco product when data are not available for the new or predicate tobacco product. In order for FDA to evaluate the surrogate tobacco product for its suitability (i.e., whether the data for the surrogate tobacco product can be extrapolated to the new or predicate tobacco product), you should provide detailed information about a tobacco product's characteristics, including design parameters, ingredients, tobacco blend, and component composition. An SE Report may include a surrogate new tobacco product, a surrogate predicate tobacco product, or both. If there is insufficient data to justify using a product as a surrogate, FDA cannot issue an SE order (assuming that this data is necessary to demonstrate 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).

As an example, an SE Report for a cigarette may include HPHC data for a surrogate 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 HPHC quantities. In this example, the SE Report should include tobacco blend information for the predicate and surrogate predicate tobacco products demonstrating that the products have identical blends (e.g., identical tobacco and additives in the filler). The applicant could indicate that, because of the identical blends, tobacco-specific nitrosamine (TSNA) filler data for the surrogate predicate tobacco product can be extrapolated to the predicate tobacco product.

Adequate Tobacco and Ingredient Information

Your SE Report should provide information about tobacco and other ingredients in all components of the new and predicate tobacco products. The information provided for all ingredients should include sufficient detail to fully identify the composition of the new and predicate tobacco products. Your SE Report should provide a detailed list of ingredients in the new and predicate tobacco products including the following:

- Ingredient names and absolute quantities (e.g., mg/cigarette) for all components
- Single ingredient names and absolute quantities in each complex ingredient (including reconstituted tobacco)
- Uniquely identifying information for all tobacco (e.g., tobacco type)
- Uniquely identifying information for all ingredients (e.g., CAS #, function)

If your SE Report contains ingredient quantities that are reported with values such as "less than", "<", "NA", "N/A", "blank", or "shaded quantities" (e.g., shaded cells in Excel spreadsheets), additional explanation of the meaning of these values should be provided. Because what is being reported may be unclear, it would be helpful to provide justification for reporting these types of values in your SE Report.

Complex Ingredients

When providing a list of ingredients, you should provide full information regarding complex ingredients. For example, your SE Report should provide the names, functions, and quantities (mg/cigarette) of the single ingredients that comprise the complex ingredient (e.g., a flavoring mixture or casing). It is important to distinguish between complex ingredients made to your specifications and those that are

not. For all complex ingredients made to your specifications, you should provide complete information according to FDA's Guidance for Industry Listing of Ingredients in Tobacco Products. For complex ingredients that are not made to your specifications, you should provide complete information on the single ingredients that comprise these complex ingredients. If applicable, we suggest that you work with your ingredient supplier to submit a tobacco product master file (TPMF) so that FDA can determine whether differences in these complex ingredients cause the new tobacco product to raise different questions of public health. Additionally, for all complex ingredients, you should ensure that the comprising single ingredient quantities add up to 100%.

Referencing a Tobacco Product Master File (TPMF)

A Tobacco Product Master File (TPMF) is submitted information that may be referenced by an authorized party in support of an application. When relying on information in a TPMF, your SE Report should reference the TPMF, cite the TPMF submission tracking number (STN), and cite the owner of the TPMF. Additionally, your submission should include a letter of authorization (LOA) from the TPMF owner allowing FDA to review the information in the TPMF.

Use of Studies that Don't Include the New and Predicate Products

If referencing research studies, you should explain how each reference supports the specific comparison between the new and predicate products. You should provide a rationale explaining how data generated using the experimental cigarettes evaluated in these references can be extrapolated to the new and predicate products subject of your SE Report, taking into account cigarette composition, smoke dilution methods, in vitro and in vivo exposure regimens, and data analysis methods. Explain how data extrapolated from these references supports the conclusion that the different characteristics in the new product compared to the predicate product do not cause the new product to raise different questions of public health.

Addressing Toxicity Caused by Ingredient Changes

When addressing the potential effects of ingredient changes, you should account for the potential toxicity of the changed ingredient via the route of exposure (e.g., inhalation), and the effect of the changed ingredient on HPHC delivery (e.g., combustion of the ingredient to form an HPHC). For a new and predicate product comparison, there may be multiple ways to address the toxicological differences that may result from ingredient changes. Different approaches that may address ingredient changes include:

1. HPHC information showing that there are no increases in HPHC delivery in the new product relative to the predicate product.

2. Battery of in vitro studies with a supporting rationale for how the submitted studies address the human cancer risk and non-cancer hazards expected because of the HPHC increases measured in the new products. Such studies could also potentially address concerns about the possible human health effects of ingredients in their unchanged form.

3. Toxicological analyses of ingredients or HPHCs that have been or can be used to establish health protective reference values (e.g., toxicological analyses conducted by the Environmental Protection Agency or toxicological information from the European Food Safety Authority) applicable to anticipated human exposures from use of the new product and how the reference values address the toxicological effects expected from the new product's ingredients or HPHCs. Note that reference values based on non-cancer endpoints do not support carcinogenic HPHCs. In the absence of compelling data supporting a dose threshold below which the carcinogenicity of a compound definitively does not occur, it is a standard assumption and toxicological practice to assume a linear relationship between the dose of a carcinogen and an increased risk of cancer.

In these analyses, it is important to account for the following parameters:

- Route of administration in study compared to route of exposure from use of the new and predicate products
- Relevance of animal species tested
- Dose-response profile
- Exposure frequency and duration
- Identifiers of adverse or critical effects, point of departure (e.g., no observable adverse effect level (NOAEL), lowest observable adverse effect level (LOAEL))
- Biological significance of response
- Relevance of uncertainty factors used
- Adjustment of the critical effect level to the dose metric of interest
- Species strain- and sex-specific effects
- Interpretation of results
- Availability of supporting evidence (e.g., read-across of toxicity data using structure-activity relationships, computational structure-activity relationship models with human expert interpretation to predict toxicity) and relevance of results to humans
- Available information on the metabolic fate and disposition of ingredients

Fermentation Process

If your new or predicate tobacco product contains fermented tobacco, we need information about the fermentation process because fermentation can result in different degrees of change in the chemical constituents of the tobacco as well as impact the microbial content of the final product. Your SE Report should provide the following information regarding the fermentation process:

1. Duration of fermentation
2. Fermentation conditions (e.g., pH, temperature, humidity)
3. Microbial characterization data (including species name and inoculum concentration) of the fermentation inoculum/starter cultures, if applicable
4. Ingredients added during the fermentation process that would impact the microbial stability of the product, if applicable

5. Method used to stabilize or stop fermentation (e.g., heat treatment), if applicable, including the parameters of the method (e.g., length of treatment, temperature)
6. Storage conditions of the final products prior to packaging

If any parameters differ between the new and predicate tobacco products, explain why those differences do not cause the new tobacco product to raise different questions of public health.

Heat Treatment Process

If your new or predicate tobacco product is heat treated, information is needed on the heat treatment process. You should provide the type of heat treatment used, the process parameters (e.g., temperature, exposure time), and validation information for the heat treatment process. If there are any differences in the processing of the new and predicate tobacco products, explain why those differences do not cause the new tobacco product to raise different questions of public health.

Nicotine Quantity

Your SE Report should provide the nicotine quantity in both the new and predicate tobacco products. Because nicotine is an addictive component of all tobacco products, comparative data for this ingredient is critical to allow FDA to make a determination of potential impact on public health. You should provide data on the total nicotine content of the new tobacco product based on at least three measurements. If the nicotine content or nicotine smoke yield is different between the new and predicate tobacco products, you should provide scientific evidence to demonstrate that the increase or decrease in nicotine content does not cause the new tobacco product to raise different questions of public health relating to tobacco addiction.

Use of Interchangeable Materials

If you select new or predicate tobacco products that are composed of interchangeable materials, each unique combination of ingredients is considered a unique tobacco product. In accordance with Section 910(a)(1)(B) of the FD&C Act, each product modification, including use of an alternate material, constitutes a new tobacco product. A material is an alternate material if it has any difference in composition (e.g., ingredients, additives, biological organisms) or design parameters (e.g., target specifications, range limits). Each new and predicate tobacco product must consist of a single combination of components and structural materials. Therefore, your SE Report should identify the following if the new or predicate tobacco products contain interchangeable ingredients:

1. Every unique material combination in the predicate tobacco product that you are comparing to the new tobacco product in accordance with Section 910(a)(2)(B) of the FD&C Act
2. Every unique material combination in the new tobacco product **[Insert the following sentence for *Provisional* SE Reports only]**. Each specific combination of materials will be considered a single new tobacco product and evaluated individually in accordance with Section 910(a)(2)(B) of the FD&C Act
3. A list of ingredients and ingredient quantities for each identified material in each new and predicate tobacco product
4. Target specifications and upper and lower range limits for all design parameters for each material in each new and predicate tobacco product

5. Test data (i.e., measured values of design parameters), including test protocols, quantitative acceptance criteria, data sets, and a summary of results. All of this information should be provided for any design parameter that differs between the new and predicate tobacco products.

Certificates of analysis (COAs) from the material supplier may provide some of the information listed above. If you choose to provide COAs for any of the parameters, the COAs should include target specification, quantitative acceptance criteria, parameter units, test data average value, and the minimum and maximum values of the test data. COAs should be complete and unaltered COAs from the material supplier.

Additionally, if a difference exists between the new and predicate tobacco products, you should provide justification for the difference and a rationale for why the difference does not cause the new tobacco product to raise different questions of public health. To clearly identify the specific new and predicate tobacco products in your SE Report, some options include:

1. Identify a single unique predicate tobacco product (with corresponding ingredients) composed of a single component material (e.g., filter tow, plug wrap). Additionally, select and identify a single new tobacco product (with corresponding ingredients) composed of a single material. In this case, the new tobacco product would be the only version of the new tobacco product considered for evaluation of substantial equivalence with the identified predicate tobacco product.

2. If you need to list interchangeable materials for the new or predicate tobacco product (or both), you may choose to demonstrate that the use of interchangeable materials does not cause the new tobacco product(s) to raise different questions of public health. To do this, identify every unique new and predicate tobacco product that may result from the integration of each combination of interchangeable materials. Each identified new and predicate tobacco product should consist of a single material combination. Target specifications, upper and lower range limits, and data generated from testing of applicable design parameters and HPHCs should be provided for each unique new and predicate tobacco product.

3. If you need to list interchangeable materials for the new or predicate tobacco product (or both), you may choose to provide a "bracketing" approach to demonstrate that the interchangeable materials do not cause the new tobacco product(s) to raise different questions of public health. To do this, you should specify two unique versions of the new tobacco product, and if the predicate tobacco product contains interchangeable materials, two unique versions of the predicate tobacco product:

    - For one of the unique versions of the **new** tobacco product, identify a single set of interchangeable materials that results in the **highest** HPHC yields generated through integration of the interchangeable materials.
    - For the other unique version of the **new** tobacco product, identify a single set of interchangeable materials that results in the **lowest** HPHC yields generated through integration of the interchangeable materials.
    - For one of the unique versions of the **predicate** tobacco product, identify a single set of interchangeable materials that results in the **highest** HPHC yields generated through integration of the interchangeable materials.

- For the other unique version of the **predicate** tobacco product, identify a single set of interchangeable materials that results in the **lowest** HPHC yields generated through integration of the interchangeable materials.

Provide a justification for why each version of the new and predicate tobacco products is representative of the highest and lowest HPHC yields from the products. Additionally, for each version specified, you should provide target specifications, upper and lower range limits, and data generated from testing of applicable design parameters and HPHCs for all of the identified new and predicate tobacco products.

Dissolution Study

Product design and ingredient changes to the tobacco product can affect the nicotine release rate and total nicotine released from the tobacco product. In cases where there are differences in design parameters, as described elsewhere, in target pH values, or in ingredients such as fillers or binders (largely natural gums), you should provide adequate scientific evidence and rationale that such changes do not cause the new tobacco product to raise different questions of public health.

One way to demonstrate that the differences between the new and predicate tobacco products do not raise different questions of public health is through the measurement of nicotine release rates and total delivered content from the new and predicate tobacco products. This information could be obtained through studies of nicotine in artificial saliva (using in vitro dissolution experiments). If nicotine release data is provided, include the following:

1. Description of the dissolution apparatus (apparatus type, media volume)
2. Description of the dissolution conditions (media, temperature, stir/flow rate, etc.)
3. Description of the dissolution media (pH, buffers, enzymes, buffer capacity, degassing, etc.)
4. Description and rationale for the sampling time points (should include 3 time points in initial release period and no more than 2 time points in the steady state portion of the release curve)
5. Description of sample size and disposition (how much is added to the vessel, was a sinker used, etc.)
6. Percentage nicotine released (relative to a t∞ time point) for each data point (t∞ is determined by increasing the flow rate for a period of time after steady state is reached)
7. Percentage released vs time plots for a representative sample of the new and predicate products
8. Quantitative test protocols, description of method used, and validation that the method is suitable for dissolution samples
9. Testing laboratory and their accreditation(s)
10. Length of time between date(s) of manufacture and date(s) of testing
11. Number of replicates
12. Standard deviation(s)
13. Complete data sets
14. A summary of the results for all testing performed
15. Storage conditions prior to initiating testing

The dissolution procedures should take care to ensure that the tobacco product does not disperse during the measurement, especially for loose tobacco products (using sinkers or glass beads, as

appropriate). If your test methods are national or international test standards, identify any deviations from those standards.

Product Stability

Your SE Report should provide information about post-manufacturing product stability. This should include stability testing data for the physical and chemical attributes that affect microbial activity during product storage. In addition, explain how the expected storage time (shelf life) is determined. Provide a detailed description of all stability testing performed, including test protocols, quantitative acceptance criteria, data sets and a summary of the results. Provide the following information about post-manufacturing stability so that FDA can fully evaluate the differences between the new and predicate tobacco products:

1. pH
2. Water activity (a_w)
3. TSNAs (total, NNN, NNK)
4. Nitrate and nitrite levels
5. Preservatives and microbial metabolic inhibitor levels (if any)
6. Total aerobic microbial count
7. Total yeast and mold count

At a minimum, these parameters should be measured at the beginning (zero time), middle, and end of the expected storage time for the final tobacco product. If there are differences in any of these endpoints between the new and predicate tobacco products, explain why those differences do not cause the new tobacco product to raise different questions of public health.

HPHC Yields

It is recommended that all SE Reports contain HPHC yield data for the new and predicate tobacco products. In addition, ingredients such as sodium carbonate, potassium acetate, and ammonia can influence the pH of a smokeless tobacco product, and a change in pH can impact the amount of free nicotine released from the tobacco product. You should provide the pH of the new and predicate tobacco products and quantify the total and free nicotine quantities in the new and predicate tobacco products. Where there are differences in characteristics, you should provide scientific evidence and rationale to address why these differences do not cause the new tobacco product to raise different questions of public health. You should consider measuring HPHCs that would be impacted by the tobacco blends, ingredients, and product design in extracts obtained from the new and predicate products. The following information about HPHC and pH testing should be provided so that we can fully evaluate the differences in the new and predicate tobacco products:

1. Reference product datasets (e.g., CRP-1)
2. Complete description of quantitative test protocols, method used, and full validation studies
3. Testing laboratory and its accreditation(s)
4. Length of time between date(s) of manufacture and date(s) of testing
5. Number of replicates
6. Standard deviation(s)

7. Complete data sets
8. A summary of the results for all testing performed
9. Storage conditions prior to initiating testing

If your test methods are national or international test standards, identify any deviations from those standards.

If your predicate tobacco product is not available for testing, there are options which you may choose to pursue to try to demonstrate substantial equivalence. See above for information on surrogate tobacco products.

Use of QRA to Address HPHC Increases

A quantitative risk assessment (QRA) approach may be useful in limited situations where there are offsetting HPHC increases and decreases. Further, there are some cases in which the HPHC offsetting is so obvious that a qualitative approach may be sufficient – such as when there are sharp decreases in several high-potency carcinogens and a small increase in a carcinogen of lower potency. If there are multiple HPHC increases without concomitant HPHC decreases, a well-conducted QRA is unlikely to address the increases in toxicological hazard and risk associated with the HPHC increases. In cases where there are clear HPHC increases in the new tobacco product compared to the predicate tobacco product without offsetting HPHC decreases, a well-conducted QRA would simply reflect the difference in hazard and risk between the new and predicate tobacco products and would therefore not add support to the contention that the new tobacco product does not raise different questions of public health.

If a QRA is submitted in your SE Report, you should address whether any elevated levels of HPHCs (and other constituents of concern) in the new product, as compared to the predicate product, increase the overall cancer risk and non-cancer hazard of the new product as compared to the predicate product. The design of the QRA should outline the specific question(s) addressed by the QRA and clearly define the overall risk model. Sufficient detail is needed to adequately compare the cumulative hazard and risk for the specific new and predicate product pair. The QRA should clearly outline how specific differences between the new and predicate products change the total hazard and risk of each product. For FDA to evaluate a QRA, it should, at a minimum, include the following information:

1. A well-developed and scientifically supported risk assessment, including a problem formulation, hazard identification, dose-response assessment, exposure assessment and risk characterization, as outlined by the National Research Council.[1] Also include identification and characterization of uncertainty and variability throughout the elements of the risk assessment process

2. All raw data, equations, assumptions, parameters, outputs, and references used, and justification that the QRA is appropriate for comparing the relative human health risks and hazards from use of the new and predicate products for the relevant user population

[1] National Research Council of the National Academies, 2009. *Science and Decisions: Advancing Risk Assessment.* Washington, DC.

3. All relevant measured HPHCs or other constituents of potential toxicological concern, employing, as much as possible, a consistent risk assessment approach for all constituents being evaluated

4. Evidence that the constituents considered in the composite QRA are representative of potential differences in the cumulative hazard and risk of the new and predicate tobacco products, and evidence that the evaluation can discern a difference in hazard and risk between the new and predicate tobacco products

In vivo nonclinical studies are not required to address ingredient changes. FDA supports reducing the reliance on animal testing where adequate and scientifically valid animal alternatives can be substituted. When using any toxicology study data collected, as well as referencing any publicly available toxicology information on published research studies, you should explain how the study data or information in each reference supports a toxicological evaluation of the comparison between the new and predicate products. Aspects to consider include a rationale explaining how data generated using a specific tobacco product (e.g., experimental cigarette, reference tobacco product, or a marketed tobacco product other than the new and predicate products) evaluated in any studies or references can be extrapolated to the new and predicate products and specific product differences. This rationale should take into account cigarette composition, smoke dilution methods, in vitro and in vivo exposure regimens, and data analysis. Also, you should state the limitations of the methods used in the study. In addition, you should explain in a narrative how data extrapolated from any referenced studies support the conclusion that the different characteristics do not cause the new product to raise different questions of public health.

Use of a Model

If you choose to use a model, you should provide all design characteristics and all ingredients for all tobacco products modeled. A modeling approach is not likely to be useful in circumstances where there are many ingredient differences between the new and predicate tobacco products. Ingredient changes alter the physicochemical characteristics of a new tobacco product, especially if that tobacco product combusts, heats, or otherwise applies energy to a mixture. Therefore, ingredient changes can influence the toxicological potential of a new tobacco product relative to a predicate tobacco product. An empirical test sufficiently powered to elucidate potential differences between a new and predicate tobacco product would likely show physicochemical or toxicological differences between the new and predicate tobacco products. Similarly, a well-conducted physicochemical or toxicological model will likely show differences in health risk to the user if there are a large number of ingredient changes to the new tobacco product relative to a predicate tobacco product. FDA recommends that applicants discuss the use of any models addressing toxicity or health risks used to support an SE Report with FDA prior to the start of scientific review of the SE Report.

[INCLUDE: AMENDMENTS AND ENVIRONMENTAL ASSESSMENTS FOR ACKNOWLEGEMENT AND NOTIFICATION LETTERS ONLY. FOR ALL OTHER LETTERS CONTINUE TO THE OPTIONS SECTION BELOW]

Amendments

All information in SE Reports should be consistent between the original submission and any amendments. If you provide updated information in an amendment, FDA will consider that information

to supersede the information provided in the original submission, except for measured values (e.g., test data, HPHC data). For measured values, applicants should provide rationale for why the updated data are appropriate for consideration. If rationale is not provided, measured values will be combined with previous measured values for evaluation.

[FOR PROVISIONAL SE REPORTS, INCLUDE:]
Environmental Assessment

In general, granting an order finding a tobacco product substantially equivalent under Section 910(a)(2)(B) of the FD&C Act is a class of action that has a categorical exclusion in place and does not normally require the preparation of an environmental assessment (EA) or an environmental impact statement (EIS). However, as required under 21 CFR 25.21 and 40 CFR 1508.4, FDA will require preparation of at least an EA for any specific action that normally would be excluded if extraordinary circumstances are present such that the specific proposed action may have the potential to significantly affect the quality of the human environment. If you elect to request a categorical exclusion, it should be submitted in accordance with 21 CFR 25.15 and include:

1. A statement of compliance with the categorical exclusion criteria
2. A statement that, to the submitter's knowledge, no extraordinary circumstances exist

A statement that no extraordinary circumstances exist could read as follows: "The proposed action of finding [name of product] substantially equivalent under Section 910(a)(2)(B) of the FD&C Act is a class of actions under 21 CFR 25.35(a). The proposed action complies with the criteria for this claim of categorical exclusion. To the best of our knowledge, no extraordinary circumstances exist that require the submission of an environmental assessment or an environmental impact statement."

[END]

[FOR REGULAR SE REPORTS, INCLUDE:]
Environmental Assessment

Granting an order finding a tobacco product substantially equivalent under Section 910(a)(2)(A)(i) of the FD&C Act is not a class of action that has a categorical exclusion in place and thus requires an environmental assessment (EA). The following information is needed to determine whether to prepare an environmental impact statement (EIS) or finding of no significant impact (FONSI). An inadequate resolution of this issue may delay issuance of an order of substantial equivalence. Please consider the following information:

- When providing a bundled submission containing multiple products, a unique EA should be written for each new tobacco product.
- EAs will be available to the public in accordance with 40 CFR 1506.6.
- To assist in preparing an EA, you can review EAs that have been posted on the CTP website.
- Each EA should address the environmental effects of the new product manufacturing, use, or disposal and include the following:
    - The affected environment – Provide a description of the land use around the manufacturing facility, including an aerial photograph showing the described area and the environment where the product will be used or disposed.

- Air quality – Provide details regarding any changes in compounds emitted during manufacturing, use, and disposal (new compounds emitted and/or increases in current emissions). Discuss any environmental effects due to these changes.
- Water resources -- Discuss the potential that the new product will impact wastewater discharges and the effects on water resources.
- Land use and zoning – Discuss the potential that the product will require an expansion of the manufacturing facility and if so, the effects on land use and zoning due to that expansion.
- Biological resources -- Discuss the potential to jeopardize the continued existence of any listed species under the Endangered Species Act.
- Geological features and soils -- Discuss the potential for the new product to lead to soil changes; discuss the potential effects on land conversion of prime farmland, unique farmland, or farmland of statewide importance to non-agricultural use.
- Socioeconomics and environmental justice -- Discuss the potential to impact socioeconomics and the impacts on employment revenue or taxes.
- Solid waste and hazardous waste -- Discuss the potential to change current solid waste and hazardous waste generation, the need for new or revised waste permits, and the need for new landfill construction.
- Floodplains, wetlands and coastal zones – Discuss the potential of any land disturbance.
- Regulatory compliance -- Provide detailed information for permits for (1) air emissions, (2) storm water, and (3) wastewater. Include information on the type of permits, the permit numbers, and the expiration dates of the permits.
- Cumulative impacts – Discuss the potential that the new product will incrementally increase or change the chemicals released to the environment. Also, describe potential past, current, and foreseeable future environmental effects associated with air quality, water resources, land use and zoning, biological resources, geological features and soils, socioeconomics and environmental justice, solid waste and hazardous waste, floodplains, wetlands and coastal zones.

- Each EA should include information about the predicate product and address the following:
  - Whether the predicate product will continue to be commercially marketed in the United States. If both the new and predicate products will be manufactured for commercial distribution at the same time, the EA should describe how that will change resource use and environmental impacts.
  - Current market volume, in metric tons, for the predicate product, and market volume projections for both the new and predicate products for the first and fifth years following the issuance of a marketing order for the new product.

[END]

[OPTIONS –SELECT APPROPORATE OPTIONS BASED ON PRODCUT SUBCATEGORY TO INCLUDE IN LETTER:]

[Option 1: Use if product subcategory is Loose, Moist Snuff]

Design Parameter Information

Design parameters are foundational information that allows FDA to better understand the tobacco product and are necessary to fully characterize the new and predicate tobacco products. The design parameters necessary to control the manufacture of your tobacco product may not be sufficient to

provide the complete characterization necessary for the comparison of two products. However, those critical design parameters will provide most of the information that FDA needs. Often manufacturers maintain this type of information in technical data sheets for each product. Where these data sheets are available, you should provide them and all accompanying documentation (e.g., Certificates of Analysis (COAs), other specification documents). Where these data sheets are not available for the new and predicate tobacco products, you should provide the materials that are available. You should provide target specifications and upper and lower range limits for all of the following design parameters for each new and predicate tobacco product, submitted either within the data sheets or SE Report:

1. Tobacco particle size (provide one of the following):
    a. Procedural control of particle size
        i. Complete description of milling/cutting/sifting processes
        ii. Control parameters of miller/cutter
        iii. Sift specifications (if applicable)
        iv. Tobacco blend (% lamina and % stem)
    b. Particle size range
    c. Detailed description of other approaches used (if any)
2. Tobacco moisture (% water)

COAs from the material supplier may be appropriate to satisfy this information. If you choose to provide COAs for any of the parameters listed above, the COAs should include target specification, quantitative acceptance criteria (tolerances), parameter units, test data average value, and the minimum and maximum values of the test data. The COA should be a complete, unaltered COA from the material supplier.

If a difference exists in the target specifications or range limits between the new and predicate tobacco products, or the new tobacco product range limits are not completely encompassed by the predicate tobacco product range limits, the FDA will need additional information to evaluate your tobacco product. The additional information needed includes measurements of the design parameters (test data) of the components (or manufactured products, as appropriate), the test protocols, your quantitative acceptance criteria (what would make you reject a lot of incoming material or formulated tobacco product, relative to that parameter), test data sets, and a summary of the results for each of the design parameters that are different between the new and predicate tobacco products. For the design parameters that were tested according to national or international standards, identify the standards and state what deviations from the standards occurred (if any).

Test protocols are necessary so that FDA can determine whether the test data for the new and predicate tobacco products were collected under comparable conditions. If different test protocols were used for the new and predicate tobacco products, you should explain how the methods and in turn, the test data, may be evaluated.

Differences in the target values of any of the design parameters listed may result in differences in the nicotine release characteristics of the new and predicate tobacco products. In these cases, FDA needs scientific evidence and rationale for why any differences in tobacco cut size between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health. This evidence could be provided by dissolution studies, as described elsewhere in this letter.

If there is a difference in tobacco cut size or more than a minor difference in manufacturing process (e.g., change in cutter size setting, sieving equipment used, or other relevant process parameter) between the new and predicate tobacco products, additional information will be needed. One option is to manufacture the new tobacco product consistent with current product composition and design specifications and remanufacture the predicate tobacco product consistent with the product composition and design specifications in place at the time the original predicate tobacco product was originally manufactured. Then, test the cut size of the new tobacco product and the remanufactured predicate tobacco product and submit the data for comparison of cut size. Another option would be to select a tobacco blend and subject it to the new tobacco product manufacturing process, and then use the identical tobacco blend and subject it to the predicate tobacco product manufacturing process. After both batches have been through their respective processes, test the products from both the new tobacco product manufacturing process and the predicate tobacco product manufacturing process for tobacco cut size and submit the data for comparison of tobacco cut size.

Also, because cut size can affect constituent release, you should provide scientific evidence and rationale for why any differences in tobacco cut size between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.
[END OPTION 1]

[Option 2: Use if product subcategory is Portioned, Moist Snuff]

Design Parameter Information

Design parameters are foundational information that allows FDA to better understand the tobacco product and are necessary to fully characterize the new and predicate tobacco products. The design parameters necessary to control the manufacture of your tobacco product may not be complete enough to provide the characterization necessary for the comparison of two products. However, those critical design parameters will provide most of the information that FDA needs. Often manufacturers maintain this type of information in technical data sheets for each product. Where these data sheets are available, you should provide them and all accompanying documentation (e.g., Certificates of Analysis (COAs), other specification documents). Where these data sheets are not available for the new and predicate tobacco products, you should provide the materials that are available. You should provide target specifications and upper and lower range limits for all of the following design parameters for each new and predicate tobacco product, submitted either within the data sheets or SE Report:

1. Tobacco particle size (provide one of the following):
    a. Procedural control of particle size
        i. Complete description of milling/cutting/sifting processes
        ii. Control parameters of miller/cutter
        iii. Sift specifications (if applicable)
        iv. Tobacco blend (% lamina and % stem)
    b. Measured particle size distribution (one of the following):
        i. D10, D50, and D90 particle count or volume[2]
        ii. Median, mean, and mode values of particle size
    c. Detailed description of other approaches used (if any)
2. Tobacco moisture (% water)

[2] D10, D50, and D90 denote, respectively, 10%, 50%, and 90% of particles are smaller than the particle size indicated. For example, a D10 of 8 µm would indicate that 10% of all of the particles in the sample have a diameter of less than 8 µm.

3. Portion mass (mg)
4. Portion length (mm)
5. Portion width (mm) or seam width with pouch paper width (mm)
6. Pouch paper basis weight
7. Pouch paper porosity or permeability
    a. Pouch paper porosity for cellulose materials only (CU)
    b. Pouch paper permeability for non-woven materials only ($L/m^2/Sec$)
    c. Melt blown materials (define and provide rationale for your units)
8. Pouch paper caliper

For each of the above parameters, the data should be provided on a per unit of measurement of product basis (e.g., portion mass should be reported in milligrams per portion). If a design parameter is not applicable, state as such and provide a rationale.

COAs from the material supplier may be appropriate to satisfy this information. If you choose to provide COAs for any of the parameters listed above, the COAs must include target specification, quantitative acceptance criteria (tolerances), parameter units, test data average value, and the minimum and maximum values of the test data. The COA must be a complete, unaltered COA from the material supplier.

If a difference exists in the target specifications or range limits between the new and predicate tobacco products, or the new tobacco product range limits are not completely encompassed by the predicate tobacco product range limits, the FDA will need additional information to evaluate your tobacco product. The additional information needed includes measurements of the design parameters (test data) of the components (or manufactured products, as appropriate), the test protocols, your quantitative acceptance criteria (what would make you reject a lot of incoming material or formulated tobacco product, relative to that parameter), test data sets, and a summary of the results for each of the design parameters that are different between the new and predicate tobacco products.

The test data should be provided on a per unit of measurement of product basis (e.g., portion mass should be reported in mg per portion). For the design parameters that were tested according to national or international standards, identify the standards and state what deviations from the standards occurred (if any).

Test protocols are necessary so that FDA can determine whether the test data for the new and predicate tobacco products were collected under comparable conditions. If different test protocols were used for the new and predicate tobacco products, you should explain how the methods and in turn, the test data, may be evaluated.

In cases where the new and predicate tobacco products have different target values, use different pouch materials (i.e., cellulose vs non-woven), have different tobacco particle size or distribution, or have differences in any of the other design parameters listed, this may result in differences in the nicotine release characteristics of the new and predicate tobacco products. In these cases, FDA needs dissolution profiles and measurements as described elsewhere in this letter to evaluate the effects of the differences in the design parameters.
[END OPTION 2]

[Option 3: Use if product subcategory is Loose Snus]

Design Parameter Information

Design parameters are foundational information that allows FDA to better understand the tobacco product and are necessary to fully characterize the new and predicate tobacco products. The design parameters necessary to control the manufacture of your tobacco product may not be sufficient to provide the complete characterization necessary for the comparison of two products. However, those critical design parameters will provide most of the information that FDA needs. Often manufacturers maintain this type of information in technical data sheets for each product. Where these data sheets are available, you should provide them and all accompanying documentation (e.g., Certificates of Analysis (COAs), other specification documents). Where these data sheets are not available for the new and predicate tobacco products, you should provide the materials that are available. You should provide target specifications and upper and lower range limits for all of the following design parameters for each new and predicate tobacco product, submitted either within the data sheets or SE Report:

1. Tobacco particle size (provide one of the following):
    a. Procedural control of particle size
        i. Complete description of milling/cutting/sifting processes
        ii. Control parameters of miller/cutter
        iii. Sift specifications (if applicable)
        iv. Tobacco blend (% lamina and % stem)
    b. Measured particle size distribution (one of the following):
        i. D10, D50, and D90[3] particle count or volume
        ii. Median, mean, and mode vales of particle size
    c. Detailed description of other approaches used (if any)
2. Tobacco moisture (% water)

COAs from the material supplier may be appropriate to satisfy this information. If you choose to provide COAs for any of the parameters listed above, the COAs must include target specification, quantitative acceptance criteria (tolerances), parameter units, test data average value, and the minimum and maximum values of the test data. The COA must be a complete, unaltered COA from the material supplier.

If a difference exists in the target specifications or range limits between the new and predicate tobacco products, or the new tobacco product range limits are not completely encompassed by the predicate tobacco product range limits, the FDA will need additional information to evaluate your tobacco product. The additional information needed includes measurements of the design parameters (test data) of the components (or manufactured products, as appropriate), the test protocols, your quantitative acceptance criteria (what would make you reject a lot of incoming material or formulated tobacco product, relative to that parameter), test data sets, and a summary of the results for each of the design parameters that are different between the new and predicate tobacco products. For the design parameters that were tested according to national or international standards, identify the standards and state what deviations from the standards occurred (if any).

Test protocols are necessary so that FDA can determine whether the test data for the new and predicate tobacco products were collected under comparable conditions. If different test protocols were used for

[3] D10, D50, and D90 denote, respectively, 10%, 50%, and 90% of particles are smaller than the particle size indicated. For example, a D10 of 8 µm would indicate that 10% of all of the particles in the sample have a diameter of less than 8 µm.

the new and predicate tobacco products, you should explain how the methods and in turn, the test data, may be evaluated.

Differences in the target values of any of the design parameters listed may result in differences in the nicotine release characteristics of the new and predicate tobacco products. In these cases, FDA needs scientific evidence and rationale for why any differences in tobacco cut size between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health. This evidence could be provided by dissolution studies, as described elsewhere in this letter.

If there is a difference in tobacco cut size or more than a minor difference in manufacturing process (e.g., change in cutter size setting, sieving equipment used, or other relevant process parameter) between the new and predicate tobacco products, additional information will be needed. One option is to manufacture the new tobacco product consistent with current product composition and design specifications and remanufacture the predicate tobacco product consistent with the product composition and design specifications in place at the time the original predicate tobacco product was originally manufactured. Then, test the cut size of the new tobacco product and the remanufactured predicate tobacco product and submit the data for comparison of cut size. Another option would be to select a tobacco blend and subject it to the new tobacco product manufacturing process, and then use the identical tobacco blend and subject it to the predicate tobacco product manufacturing process. After both batches have been through their respective processes, test the products from both the new tobacco product manufacturing process and the predicate tobacco product manufacturing process for tobacco cut size and submit the data for comparison of tobacco cut size.

Also, because cut size can affect constituent release, you should provide scientific evidence and rationale for why any differences in tobacco cut size between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.
[END OPTION 3]

[Option 4: Use if product subcategory is Portioned Snus]

Design Parameter Information

Design parameters are foundational information that allows FDA to better understand the tobacco product and are necessary to fully characterize the new and predicate tobacco products. The design parameters necessary to control the manufacture of your tobacco product may not be sufficient to provide the complete characterization necessary for the comparison of two products. However, those critical design parameters will provide most of the information that FDA needs. Often manufacturers maintain this type of information in technical data sheets for each product. Where these data sheets are available, you should provide them and all accompanying documentation (e.g., Certificates of Analysis (COAs), other specification documents). Where these data sheets are not available for the new and predicate tobacco products, you should provide the materials that are available. You should provide target specifications and upper and lower range limits for all of the following design parameters for each new and predicate tobacco product, submitted either within the data sheets or SE Report:

1. Tobacco particle size (provide one of the following):
    a. Procedural control of particle size
        i. Complete description of milling/cutting/sifting processes
        ii. Control parameters of miller/cutter
        iii. Sift specifications (if applicable)

        iv. Tobacco blend (% lamina and % stem)
    b. Measured particle size distribution (one of the following):
        i. D10, D50, and D90 particle count or volume[4]
        ii. Median, mean, and mode vales of particle size
    c. Detailed description of other approaches used (if any)
2. Tobacco moisture (% water)
3. Portion mass (mg)
4. Portion length (mm)
5. Portion width (mm) or seam width with pouch paper width (mm)
6. Pouch paper basis weight
7. Pouch paper porosity or permeability
    a. Pouch paper porosity for cellulose materials only (CU)
    b. Pouch paper permeability for non-woven materials only ($L/m^2/Sec$)
    c. Melt blown materials (define and justify your units)
8. Pouch paper caliper

For each of the above parameters, the data should be provided on a per unit of measurement of product basis (e.g., portion mass should be reported in milligrams per portion). If a design parameter is not applicable, state as such and provide a rationale.

COAs from the material supplier may be appropriate to satisfy this information. If you choose to provide COAs for any of the parameters listed above, the COAs must include target specification, quantitative acceptance criteria (tolerances), parameter units, test data average value, and the minimum and maximum values of the test data. The COA must be a complete, unaltered COA from the material supplier.

If a difference exists in the target specifications or range limits between the new and predicate tobacco products, or the new tobacco product range limits are not completely encompassed by the predicate tobacco product range limits, the FDA will need additional information to evaluate your tobacco product. The additional information needed includes measurements of the design parameters (test data) of the components (or manufactured products, as appropriate), the test protocols, your quantitative acceptance criteria (what would make you reject a lot of incoming material or formulated tobacco product, relative to that parameter), test data sets, and a summary of the results for each of the design parameters that are different between the new and predicate tobacco products.

The test data should be provided on a per unit of measurement of product basis (e.g., portion mass should be reported in mg per portion). For the design parameters that were tested according to national or international standards, identify the standards and state what deviations from the standards occurred (if any).

Test protocols are necessary so that FDA can determine whether the test data for the new and predicate tobacco products were collected under comparable conditions. If different test protocols were used for the new and predicate tobacco products, you should explain how the methods and in turn, the test data, may be evaluated.

[4] D10, D50, and D90 denote, respectively, 10%, 50%, and 90% of particles are smaller than the particle size indicated. For example, a D10 of 8 µm would indicate that 10% of all of the particles in the sample have a diameter of less than 8 µm.

In cases where the new and predicate tobacco products have different target values, use different pouch materials (i.e., cellulose vs non-woven), have different tobacco particle size or distribution, or have differences in any of the other design parameters listed, this may result in differences in the nicotine release characteristics of the new and predicate tobacco products. In these cases, FDA needs dissolution profiles and measurements as described elsewhere in this letter to evaluate the effects of the differences in the design parameters.
[END OPTION 4]

[Option 5: Use if product subcategory is Loose, Dry Snuff]

Design Parameter Information

Design parameters are foundational information that allows FDA to better understand the tobacco product and are necessary to fully characterize the new and predicate tobacco products. The design parameters necessary to control the manufacture of your tobacco product may not be sufficient to provide the complete characterization necessary for the comparison of two products. However, those critical design parameters will provide most of the information that FDA needs. Often manufacturers maintain this type of information in technical data sheets for each product. Where these data sheets are available, you should provide them and all accompanying documentation (e.g., Certificates of Analysis (COAs), other specification documents). Where these data sheets are not available for the new and predicate tobacco products, you should provide the materials that are available. You should provide target specifications and upper and lower range limits for all of the following design parameters for each new and predicate tobacco product, submitted either within the data sheets or SE Report:

1. Tobacco particle size (provide one of the following):
    a. Procedural control of particle size
        i. Complete description of milling/cutting/sifting processes
        ii. Control parameters of miller/cutter
        iii. Sift specifications (if applicable)
        iv. Tobacco blend (% lamina and % stem)
    b. Measured particle size distribution (one of the following):
        i. D10, D50, and D90[5] particle count or volume
        ii. Median, mean, and mode values of particle size
    c. Detailed description of other approaches used (if any)
2. Tobacco moisture (% water)

COAs from the material supplier may be appropriate to satisfy this information. If you choose to provide COAs for any of the parameters listed above, the COAs must include target specification, quantitative acceptance criteria (tolerances), parameter units, test data average value, and the minimum and maximum values of the test data. The COA must be a complete, unaltered COA from the material supplier.

If a difference exists in the target specifications or range limits between the new and predicate tobacco products, or the new tobacco product range limits are not completely encompassed by the predicate tobacco product range limits, the FDA will need additional information to evaluate your tobacco product. The additional information needed includes measurements of the design parameters (test

[5] D10, D50, and D90 denote, respectively, 10%, 50%, and 90% of particles are smaller than the particle size indicated. For example, a D10 of 8 µm would indicate that 10% of all of the particles in the sample have a diameter of less than 8 µm.

data) of the components (or manufactured products, as appropriate), the test protocols, your quantitative acceptance criteria (what would make you reject a lot of incoming material or formulated tobacco product, relative to that parameter), test data sets, and a summary of the results for each of the design parameters that are different between the new and predicate tobacco products. For the design parameters that were tested according to national or international standards, identify the standards and state what deviations from the standards occurred (if any).

Test protocols are necessary so that FDA can determine whether the test data for the new and predicate tobacco products were collected under comparable conditions. If different test protocols were used for the new and predicate tobacco products, you should explain how the methods and in turn, the test data, may be evaluated.

Differences in the target values of any of the design parameters listed may result in differences in the nicotine release characteristics of the new and predicate tobacco products. In these cases, FDA needs scientific evidence and rationale for why any differences in tobacco cut size between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health. This evidence could be provided by dissolution studies, as described elsewhere in this letter.

If there is a difference in tobacco cut size or more than a minor difference in manufacturing process (e.g., change in cutter size setting, sieving equipment used, or other relevant process parameter) between the new and predicate tobacco products, additional information will be needed. One option is to manufacture the new tobacco product consistent with current product composition and design specifications and remanufacture the predicate tobacco product consistent with the product composition and design specifications in place at the time the original predicate tobacco product was originally manufactured. Then, test the cut size of the new tobacco product and the remanufactured predicate tobacco product and submit the data for comparison of cut size. Another option would be to select a tobacco blend and subject it to the new tobacco product manufacturing process, and then use the identical tobacco blend and subject it to the predicate tobacco product manufacturing process. After both batches have been through their respective processes, test the products from both the new tobacco product manufacturing process and the predicate tobacco product manufacturing process for tobacco cut size and submit the data for comparison of tobacco cut size.

Also, because cut size can affect constituent release, you should provide scientific evidence and rationale for why any differences in tobacco cut size between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.
[END OPTION 5]

[Option 6: Use if product subcategory is Dissolvable]
Design Parameter Information

Design parameters are foundational information that allows FDA to better understand the tobacco product and are necessary to fully characterize the new and predicate tobacco products. The design parameters necessary to control the manufacture of your tobacco product may not be sufficient to provide the complete characterization necessary for the comparison of two products. However, those critical design parameters will provide most of the information that FDA needs. Often manufacturers maintain this type of information in technical data sheets for each product. Where these data sheets are available, you should provide them and all accompanying documentation (e.g., Certificates of Analysis (COAs), other specification documents). Where these data sheets are not available for the new and predicate tobacco products, you should provide the materials that are available. You should

provide target specifications and upper and lower range limits for all of the following design parameters for each new and predicate tobacco product, submitted either within the data sheets or SE Report:

1. Tobacco particle size (provide one of the following):
    a. Procedural control of particle size
        i. Complete description of milling/cutting/sifting processes
        ii. Control parameters of miller/cutter
        iii. Sift specifications (if applicable)
        iv. Tobacco blend (% lamina and % stem)
    b. Measured particle size distribution (one of the following):
        i. D10, D50, and D90[6] particle count or volume
        ii. Median, mean, and mode values of particle size
    c. Detailed description of other approaches used (if any)
2. Tobacco moisture (% water)

COAs from the material supplier may be appropriate to satisfy this information. If you choose to provide COAs for any of the parameters listed above, the COAs must include target specification, quantitative acceptance criteria (tolerances), parameter units, test data average value, and the minimum and maximum values of the test data. The COA must be a complete, unaltered COA from the material supplier.

If a difference exists in the target specifications or range limits between the new and predicate tobacco products, or the new tobacco product range limits are not completely encompassed by the predicate tobacco product range limits, the FDA will need additional information to evaluate your tobacco product. The additional information needed includes measurements of the design parameters (test data) of the components (or manufactured products, as appropriate), the test protocols, your quantitative acceptance criteria (what would make you reject a lot of incoming material or formulated tobacco product, relative to that parameter), test data sets, and a summary of the results for each of the design parameters that are different between the new and predicate tobacco products. For the design parameters that were tested according to national or international standards, identify the standards and state what deviations from the standards occurred (if any).

Test protocols are necessary so that FDA can determine whether the test data for the new and predicate tobacco products were collected under comparable conditions. If different test protocols were used for the new and predicate tobacco products, you should explain how the methods and in turn, the test data, may be evaluated.

Differences in the target values of any of the design parameters listed may result in differences in the nicotine release characteristics of the new and predicate tobacco products. In these cases, FDA needs scientific evidence and rationale for why any differences in tobacco cut size between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health. This evidence could be provided by dissolution studies, as described elsewhere in this letter.

If there is a difference in tobacco cut size or more than a minor difference in manufacturing process (e.g., change in cutter size setting, sieving equipment used, or other relevant process parameter)

[6] D10, D50, and D90 denote, respectively, 10%, 50%, and 90% of particles are smaller than the particle size indicated. For example, a D10 of 8 µm would indicate that 10% of all of the particles in the sample have a diameter of less than 8 µm.

between the new and predicate tobacco products, additional information will be needed. One option is to manufacture the new tobacco product consistent with current product composition and design specifications and remanufacture the predicate tobacco product consistent with the product composition and design specifications in place at the time the original predicate tobacco product was originally manufactured. Then, test the cut size of the new tobacco product and the remanufactured predicate tobacco product and submit the data for comparison of cut size. Another option would be to select a tobacco blend and subject it to the new tobacco product manufacturing process, and then use the identical tobacco blend and subject it to the predicate tobacco product manufacturing process. After both batches have been through their respective processes, test the products from both the new tobacco product manufacturing process and the predicate tobacco product manufacturing process for tobacco cut size and submit the data for comparison of tobacco cut size.

Also, because cut size can affect constituent release, you should provide scientific evidence and rationale for why any differences in tobacco cut size between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.
[END OPTION 6]

[Option 7: Use if product subcategory is Loose Chewing Tobacco]
Design Parameter Information

Design parameters are foundational information that allows FDA to better understand the tobacco product and are necessary to fully characterize the new and predicate tobacco products. The design parameters necessary to control the manufacture of your tobacco product may not be sufficient to provide the complete characterization necessary for the comparison of two products. However, those critical design parameters will provide most of the information that FDA needs. Often manufacturers maintain this type of information in technical data sheets for each product. Where these data sheets are available, you should provide them and all accompanying documentation (e.g., Certificates of Analysis (COAs) and other specification documents). Where these data sheets are not available for the new and predicate tobacco products, you should provide the materials that are available. You should provide target specifications and upper and lower range limits for all of the following design parameters for each new and predicate tobacco product, submitted either within the data sheets or SE Report:

1. Tobacco particle size (provide one of the following):
    a. Procedural control of particle size
        i. Complete description of milling/cutting/sifting processes
        ii. Control parameters of miller/cutter
        iii. Sift specifications (if applicable)
        iv. Tobacco blend (% lamina and % stem)
    b. Particle size range
    c. Detailed description of other approaches used (if any)
2. Tobacco moisture (% water)

COAs from the material supplier may be appropriate to satisfy this information. If you choose to provide COAs for any of the parameters listed above, the COAs must include target specification, quantitative acceptance criteria (tolerances), parameter units, test data average value, and the minimum and maximum values of the test data. The COA must be a complete, unaltered COA from the material supplier.

If a difference exists in the target specifications or range limits between the new and predicate tobacco products, or the new tobacco product range limits are not completely encompassed by the predicate tobacco product range limits, the FDA will need additional information to evaluate your tobacco product. The additional information needed includes measurements of the design parameters (test data) of the components (or manufactured products, as appropriate), the test protocols, your quantitative acceptance criteria (what would make you reject a lot of incoming material or formulated tobacco product, relative to that parameter), test data sets, and a summary of the results for each of the design parameters that are different between the new and predicate tobacco products. For the design parameters that were tested according to national or international standards, identify the standards and state what deviations from the standards occurred (if any).

Test protocols are necessary so that FDA can determine whether the test data between the new and predicate tobacco products were collected under comparable conditions. If different test protocols were used for the new and predicate tobacco products, you should explain how the methods and in turn, the test data, may be evaluated.

Differences in the target values of any of the design parameters listed may result in differences in the nicotine release characteristics of the new and predicate tobacco products. In these cases, FDA needs scientific evidence and rationale for why any differences in tobacco cut size between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health. This evidence could be provided by dissolution studies, as described elsewhere in this letter.

If there is a difference in tobacco cut size or more than a minor difference in manufacturing process (i.e., change in cutter size setting, sieving equipment used, or other relevant process parameter) between the new and predicate tobacco products, additional information will be needed. One option is to manufacture the new tobacco product consistent with current product composition and design specifications and remanufacture the predicate tobacco product consistent with the product composition and design specifications in place at the time the original predicate tobacco product was originally manufactured. Then, test the cut size of the new tobacco product and the remanufactured predicate tobacco product and submit the data for comparison of cut size. Another option would be to select a tobacco blend and subject it to the new tobacco product manufacturing process, and then use the identical tobacco blend and subject it to the predicate tobacco product manufacturing process. After both batches have been through their respective processes, test the products from both the new tobacco product manufacturing process and the predicate tobacco product manufacturing process for tobacco cut size and submit the data for comparison of tobacco cut size.

Also, because cut size can affect constituent release, you should provide scientific evidence and rationale for why any differences in tobacco cut size between the new and predicate tobacco products do not cause the new tobacco product to raise different questions of public health.
[END OPTION 7]

[Option 8: Use if product subcategory is Portioned Chewing Tobacco]
Design Parameter Information

Design parameters are foundational information that allows FDA to better understand the tobacco product and are necessary to fully characterize the new and predicate tobacco products. The design parameters necessary to control the manufacture of your tobacco product may not be complete enough to provide the characterization necessary for the comparison of two products. However, those critical design parameters will provide most of the information that FDA needs. Often manufacturers maintain

this type of information in technical data sheets for each product. Where these data sheets are available, you should provide them and all accompanying documentation (often technical data sheets include references to Certificates of Analysis (COAs) and other specification documents). Where these data sheets are not available for the new and predicate tobacco products, you should provide the materials that are available. You should provide target specifications and upper and lower range limits for all of the following design parameters for each new and predicate tobacco product, submitted either within the data sheets or SE Report:

1. Tobacco particle size (provide one of the following):
    a. Procedural control of particle size
        i. Complete description of milling/cutting/sifting processes
        ii. Control parameters of miller/cutter
        iii. Sift specifications (if applicable)
        iv. Tobacco blend (% lamina and % stem)
    b. Measured particle size distribution (one of the following):
        i. D10, D50, and D90 particle count or volume[7]
        ii. Median, mean, and mode vales of particle size
    c. Detailed description of other approaches used (if any)
2. Tobacco moisture (% water)
3. Portion mass (mg)
4. Portion length (mm)
5. Portion width (mm) or seam width with pouch paper width (mm)
6. Pouch paper basis weight (if applicable)
7. Pouch paper porosity or permeability (if applicable)
    a. Pouch paper porosity (for cellulose materials only) (CU)
    b. Pouch paper permeability (for non-woven materials only) ($L/m^2/Sec$)
    c. Melt blown materials (define and justify your units)
8. Pouch paper caliper (if applicable)

For each of the above parameters, the data should be provided on a per unit of measurement of product basis (e.g., portion mass should be reported in milligrams per portion). If a design parameter is not applicable, state as such and provide a rationale.

COAs from the material supplier may be appropriate to satisfy this information. If you choose to provide COAs for any of the parameters listed above, the COAs must include target specification, quantitative acceptance criteria (tolerances), parameter units, test data average value, and the minimum and maximum values of the test data. The COA must be a complete, unaltered COA from the material supplier.

If a difference exists in the target specifications or range limits between the new and predicate tobacco products, or the new tobacco product range limits are not completely encompassed by the predicate tobacco product range limits, the FDA will need additional information to evaluate your tobacco product. The additional information needed includes measurements of the design parameters (test data) of the components (or manufactured products, as appropriate), the test protocols, your quantitative acceptance criteria (what would make you reject a lot of incoming material or formulated

[7] D10, D50, and D90 denote, respectively, 10%, 50%, and 90% of particles are smaller than the particle size indicated. For example, a D10 of 8 µm would indicate that 10% of all of the particles in the sample have a diameter of less than 8 µm.

tobacco product, relative to that parameter), test data sets, and a summary of the results for each of the design parameters that are different between the new and predicate tobacco products.

The test data should be provided on a per unit of measurement of product basis (e.g., portion mass should be reported in mg per portion). For the design parameters that were tested according to national or international standards, identify the standards and state what deviations from the standards occurred (if any).

Test protocols are necessary so that FDA can determine whether the test data for the new and predicate tobacco products were collected under comparable conditions. If different test protocols were used for the new and predicate tobacco products, you should explain how the methods and in turn, the test data, may be evaluated.

In cases where the new and predicate products have different target values, use different pouch materials (i.e., cellulose vs non-woven), have different tobacco particle size or distribution, or have differences in any of the other design parameters listed, this may result in differences in the nicotine release characteristics of the new and predicate tobacco products. In these cases, FDA needs dissolution profiles and measurements, as described elsewhere in this letter to evaluate the effects of the differences in the design parameters.
[END OPTION 8]

[END OPTIONS]