SE REPORT CONTENT

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AGENDA

- SE Report overview and content
- Common deficiencies:
  A. Predicate tobacco product issues
  B. Ingredient review issues
  C. Constituent reporting issues
  D. Product design review issues
  E. Harmful and potentially harmful constituent analysis issues
- Summary

SE REPORT OVERVIEW AND CONTENT

SE REPORT OVERVIEW

- The FD&C Act, as amended by the Tobacco Control Act, requires that before a new tobacco product may be introduced into interstate commerce for commercial distribution in the United States, the new tobacco product must undergo premarket review by FDA
  - One premarket review pathway is the submission of a report under section 905(j)(1)(A)

- A SE Report is a submission under section 905(j)(1)(A)(i) of the FD&C Act that includes the basis for the applicant's determination that a new tobacco product is **substantially equivalent** to a predicate tobacco product
  - The SE Report includes the initial SE Report and all subsequent amendments

- Since 2010, FDA has received more than 5,000 premarket tobacco product applications, most of which have been SE Reports

SE REPORT SHOULD CONTAIN:

1. General information
   - Unique identification of **both** the new and predicate tobacco products
   - Evidence that the predicate tobacco product is grandfathered or previously found SE
2. Summary
3. Comparison of the characteristics of the new and predicate tobacco products
4. Testing information on the characteristics of the new and predicate tobacco products
5. Statement of compliance with applicable tobacco product standards
6. Health information summary or statement regarding availability of such information
7. Environmental assessment (EA) or a valid claim of a categorical exclusion

SE REPORT CONTENT TO FACILITATE FDA REVIEW

It has facilitated FDA review when the SE Report provides:

- A side-by-side listing of tobacco types and sub-types in a table
- Unit of measure, target and range for each tobacco type
- Description of tobacco grading system

Tobacco Type	Sub-component	Unit of Measure	New Tobacco Product			Predicate Tobacco Product		
			Lower Limit	Target	Upper Limit	Lower Limit	Target	Upper Limit
Burley	Lamina	mg/g	17.5	18.0	18.5	17.5	18.0	18.5
Burley	Stems	mg/g	4.5	5.0	5.5	4.5	5.0	5.5
Dark Air-Cured		mg/g	225	235	245	225	235	245
Reconstituted Tobacco	*	mg/g	40	50	60	40	50	60
Fermented Tobacco		mg/g	0.75	1.0	1.25	0.75	1.0	1.25

SE REPORT CONTENT TO FACILITATE FDA REVIEW

It has facilitated FDA review when the SE Report provides:

- A side-by-side listing of ingredients in a table
- Ingredient CAS number, function, and unit of measure
- Target and range for each ingredient

Ingredient	CAS No.	Function	Unit of Measure	New Tobacco Product			Predicate Tobacco Product		
				Lower Limit	Target	Upper Limit	Lower Limit	Target	Upper Limit
Ethyl alcohol denatured, SDA-4	N/A	Solvent, Processing Aid	mg/cigarette	2.1	2.3	2.5	2.7	2.9	3.1
Glycerol	56-81-5	Humectant	mg/cigarette	11.0	13.0	15.0	12.0	14.0	16.0
L-menthol	2216-51-5	Flavor	mg/cigarette	4.0	5.0	6.0	3.5	4.5	5.5
Vanillin	121-33-5	Flavor	mg/cigarette	N/A	N/A	N/A	0.005	0.006	0.007

SE REPORT CONTENT TO FACILITATE FDA REVIEW

It has facilitated FDA review when the SE Report provides:

- A side-by-side listing of design parameters in a table
- Target and range for each design parameter
- Units of measure; same units of measure for both products

Component	Sub-component	Design Feature	Unit of Measure	New Tobacco Product			Predicate Tobacco Product		
				Lower Limit	Target	Upper Limit	Lower Limit	Target	Upper Limit
		Length	mm	97.5	98.0	98.5	97.5	98.0	98.5
Tobacco filler	Tobacco	Filler mass	g	0.72	0.76	0.80	0.78	0.82	0.86
Filter	Filter	Filter efficiency	%	64	66	68	64	66	68
Filter	Tipping paper	Ventilation	%	6	15	24	6	15	24

SE REPORT CONTENT TO FACILITATE FDA REVIEW

In addition, it has facilitated FDA review when the SE Report provides:

- A side-by-side listing of ingredients in each component in a table
- Quantity of each ingredient expressed as “mass per unit of use” (e.g., mg/cigarette)
- A listing of every difference in characteristics with an explanation of why, despite the differences, the products are substantially equivalent
- All cited references, in an appendix rather than in the body of the report
- Electronic submission

COMMON DEFICIENCIES

A. COMMON DEFICIENCIES – PREDICATE PRODUCT ISSUES

1. **Predicate tobacco product is no longer available**
2. **Manufacturer does not own the predicate tobacco product**
3. **Use of a surrogate tobacco product**

1. PREDICATE PRODUCT IS NO LONGER AVAILABLE

All SE orders are based on a comparison of a new tobacco product to a predicate tobacco product; therefore, data on the predicate tobacco product are important in order for FDA to fully compare the new and predicate tobacco products.

If a manufacturer no longer manufactures the predicate tobacco product or it is no longer available, the manufacturer still needs to fully characterize the predicate tobacco product.

FDA has encountered SE Reports that lack full predicate tobacco product characterization because the predicate tobacco product is no longer available.

1. PREDICATE PRODUCT IS NO LONGER AVAILABLE

Potential options for obtaining data on a predicate tobacco product that is no longer available include:

1. Manufacture the predicate tobacco product at present day, consistent with the product composition and design specifications of the original predicate tobacco product
   - Include design parameter documentation and data to show that the present day predicate tobacco product is reflective of the predicate tobacco product at the time of original manufacture
   - Note any differences between the present day predicate tobacco product design parameters, components, or constituents and the original predicate tobacco product
     - If there are any differences, the present day predicate tobacco product will be considered a surrogate tobacco product

1. PREDICATE PRODUCT IS NO LONGER AVAILABLE

Potential options for obtaining data on a predicate tobacco product that is no longer available include:

2. Identify another, currently available tobacco product with design parameters, components, and constituents similar to the predicate tobacco product
   - This tobacco product generally will be considered a surrogate predicate tobacco product
   - Note any differences between the surrogate predicate tobacco product design parameters, components, or constituents and the predicate tobacco product

2. MANUFACTURER DOES NOT OWN THE PREDICATE TOBACCO PRODUCT

Similarly, if a manufacturer uses a predicate tobacco product that they do not own, the manufacturer still needs to fully characterize the predicate tobacco product.

If the manufacturer does not own the predicate tobacco product, it would be helpful to submit:

1. An explanation of the means by which the supplied information was obtained
2. Certification that the new tobacco product manufacturer has access to the product composition information from the predicate tobacco product manufacturer

3. USE OF A SURROGATE TOBACCO PRODUCT

In some cases, a surrogate tobacco product may be used to supply test data for a SE Report.

What is a surrogate tobacco product?

- A surrogate tobacco product is neither the new or predicate tobacco product
  - Surrogates can be used for the predicate tobacco product, the new tobacco product, or both
  - Surrogates generally have design parameters, components, and constituents similar to the tobacco product it represents
  - A remanufactured predicate tobacco product that is identical to the original predicate tobacco product is not considered a surrogate tobacco product
- Data for the surrogate tobacco product are provided *in place of* data for the new or predicate tobacco product when those data are not available
  - Note that surrogate tobacco products may not be provided for the purpose of extrapolating target specifications and range limits from the surrogate tobacco product to the new tobacco product

3. USE OF A SURROGATE TOBACCO PRODUCT

FDA must evaluate whether data from a surrogate tobacco product can be extrapolated to the new or predicate tobacco product.

- If there are insufficient data to justify using a product as a surrogate, FDA cannot make a SE determination using those data

If using a surrogate tobacco product, the following would facilitate FDA review:

- A description of which tobacco product the surrogate product represents (e.g., predicate product)
- A justification for using the surrogate product in lieu of the predicate or new tobacco product
- A detailed description of all ingredients in the surrogate product (e.g., tobacco, cigarette paper)
- A detailed description of design parameters of the surrogate product (e.g., porosity, ventilation)
- Surrogate test data to be extrapolated to the tobacco product it represents (e.g., HPHC yields)
- Testing procedures and method validation reports for the surrogate tobacco product data

B. COMMON DEFICIENCIES – INGREDIENT REVIEW ISSUES

1. **Incomplete ingredient listings**
2. **Inadequate rationale for changes in ingredient quantities**
3. **Incomplete tobacco processing information**

1. INCOMPLETE INGREDIENT LISTINGS

SE Reports should include information on product ingredients that enables FDA to compare the new tobacco product to the predicate tobacco product.

FDA has encountered SE Reports that:

- Included information on some, but not all, product ingredients
- Did not fully identify the ingredients
  - e.g., no information on tobacco grades, ingredient grades, or ingredient purity
- Stated quantities as percentages rather than in measured amounts with units of measure
- Contained discrepancies among sections of the report in the quantities/types of ingredients
- Did not fully identify complex ingredients (e.g., a flavoring mixture or casing) or single ingredient quantities did not add up to 100%

1. INGREDIENT LISTINGS

It would facilitate FDA review to provide the following information for *each* tobacco product:

- Ingredient names, absolute quantities, and functions for all components
  - e.g., papers, adhesives, pouch materials, container-closure systems
- Uniquely identifying information for all tobacco
  - Tobacco types
  - Tobacco grading system and explanation of the grading system
- Uniquely identifying information for all ingredients added to tobacco
  - CAS #, grade/purity, function
- Single ingredient names and absolute quantities in each complex ingredient
  - Complex ingredients also include reconstituted tobacco
- Quantity of each ingredient expressed as “mass per unit of use” (e.g., mg/cigarette) rather than providing percentages

1. INGREDIENT LISTINGS – COMPLEX INGREDIENTS

Ingredients that are not single chemical substances or single types of leaf tobacco are considered complex ingredients.

It would facilitate FDA review to distinguish between complex ingredients made to your specifications and those that are not.

- If made to your specifications, provide complete information according to *FDA's Guidance for Industry Listing of Ingredients in Tobacco Products*
- If not made to your specifications, FDA requests that complete information on the single ingredients that make up the complex ingredients be provided
  - If applicable, FDA suggests that you work with your supplier to submit a tobacco product master file

2. INADEQUATE RATIONALE FOR CHANGES TO INGREDIENT QUANTITIES

It would facilitate FDA review if the SE Report explains why any increase, decrease, addition, or deletion of an ingredient does not cause the new tobacco product to raise different questions of public health.

FDA has encountered SE Reports that:

- Did not address differences in ingredient quantities between the new and predicate tobacco products
- Did not make a comparison between the ingredient quantities of the *specific* new and predicate tobacco products in the SE Report

2. CHANGES TO INGREDIENT QUANTITIES

SE Reports should provide an adequate explanation of the impact of ingredient changes on public health for the new tobacco product.

- Account for the potential toxicity of the changed ingredient(s) via the route of exposure to users
  - e.g., buccal exposure for an oral tobacco product; inhalation exposure for a cigarette
- Account for the potential effects of the changed ingredient(s) on HPHC delivery
  - e.g., combustion of the ingredient and its impact on HPHC yields in a burning cigarette

FDA has not found the following explanations of the impact of ingredient changes persuasive:

- A statement that the ingredients have been used at similar levels in other tobacco products
- A statement that the ingredients are acceptable because they are used as flavors in food, when the ingredient will be combusted

3. MISSING TOBACCO PROCESSING INFORMATION

If your new or predicate tobacco product contains fermented tobacco or is heat treated, it would facilitate FDA review to provide information about the fermentation or heat treatment process. These treatments can result in differences in the chemical constituents of the tobacco as well as impact the microbial content of the final product.

FDA has encountered SE Reports that:

- Did not specify whether the tobacco has been fermented or heat treated
- Did not provide details of processing conditions

3. TOBACCO PROCESSING INFORMATION

It would facilitate FDA review to provide the following information for *each* tobacco product that contains fermented tobacco:

- Duration of fermentation and fermentation conditions
  - e.g., pH, temperature, humidity
- Microbial characterization data of the fermentation inoculum/starter cultures (if applicable)
  - Include species name and inoculum concentration
- Ingredients added during the fermentation process that would impact the microbial stability of the product (if applicable)
- Method used to stabilize or stop fermentation (if applicable)
  - Include the parameters of the method (e.g., length of treatment, temperature)
- Storage conditions of the final product prior to packaging

3. TOBACCO PROCESSING INFORMATION

It would facilitate FDA review to provide the following for *each* tobacco product that contains heat-treated tobacco:

- Type of heat treatment used
- Process parameters
  - e.g., temperature, exposure time
- Validation information for the heat treatment process
- Explanation for why any differences in processing do not cause the new tobacco product to raise different questions of public health

C. COMMON DEFICIENCIES – CONSTITUENT REPORTING ISSUES

1. **Missing nicotine yield**
2. **Missing information on HPHC testing**
3. **Inadequate data to demonstrate product stability**

1. MISSING NICOTINE YIELD

Because nicotine is an addictive component of all tobacco products, comparative data for this ingredient is important to allow FDA to make a determination of potential impact on public health.

It would facilitate FDA review to provide the following information for *each* tobacco product:

- Data on the total nicotine yield based on at least three measurements
  - If different, it would be helpful to provide scientific evidence to demonstrate that the increase or decrease in nicotine yield does not cause the new tobacco product to raise different questions of public health relating to tobacco addiction

2. MISSING INFORMATION ON HPHC TESTING

Harmful and potentially harmful constituent (HPHC) information is usually necessary to provide a complete comparison between the new and predicate tobacco products and make a SE determination.

FDA has encountered SE Reports that provided HPHC data, but failed to include sufficient testing information, such as:

- HPHC data for the predicate tobacco product
- Quantitative methods used
- Testing laboratory accreditation
- Standard deviations
- Complete data sets for all tobacco products
- Method validation parameters (e.g., accuracy, precision, robustness)

2. INFORMATION ON HPHC TESTING

It would facilitate FDA review to provide HPHC testing information for *both* the new and predicate tobacco products.

Consider measuring HPHCs that would be impacted by differences in tobacco blends, ingredients, and product design of the new and predicate tobacco products.

- For cigarettes, it is helpful to evaluate mainstream smoke produced by the new and predicate tobacco products under both ISO and Canadian Intense smoking regimens
- For smokeless tobacco, it is helpful to evaluate extracts obtained from the new and predicate tobacco products

If there are differences between the testing carried out for the new and predicate tobacco products (e.g., different test methods), it would facilitate FDA review to identify those differences and explain why data for the new and predicate tobacco products can be evaluated despite the differences.

2. INFORMATION ON HPHC TESTING

It would facilitate FDA review to provide the following information for *each* tobacco product:

- Complete data sets for all tobacco products, including:
  - A summary of the results for all testing performed
  - Number of replicates tested
  - Standard deviation(s)
  - Reference product data sets (e.g., 1R6F, CRP-1)
- Complete description of quantitative test protocols and methods used, including:
  - Testing laboratory and their accreditation(s)
  - Method validation status, and validation reports and data for each analytical method
  - Length of time between date(s) of manufacture and date(s) of testing
  - Storage conditions prior to initiating testing

2. INFORMATION ON HPHC TESTING

FDA suggests that appropriate measures be taken to minimize data variability and systematic bias in HPHC testing. Suggested measures include:

- Using the same laboratory
- Using the same methods
- Using the same type of smoking machine (when applicable)
- Testing within a similar timeframe
- Similar sample storage conditions and duration

If your test methods are national or international test standards, it would facilitate FDA review to identify any deviations from those standards.

3. INADEQUATE DATA TO DEMONSTRATE PRODUCT STABILITY

It is important to include stability information for the following types of tobacco products because the manufacturing process, storage conditions, and length of time on a shelf can affect their characteristics:

- Smokeless tobacco products
- Products that contain fermented tobacco

FDA has encountered SE Reports that failed to provide full stability data, such as:

- Stability data over the entire shelf life of the product
- Stability data for the predicate tobacco product
- Water activity (a_w)
- Tobacco-specific nitrosamine (TSNA) levels
- Microbial counts (bacteria, yeast, and mold)

3. PRODUCT STABILITY

It would facilitate FDA review to provide the following information for *each* tobacco product:

- Stability data over the entire shelf life of the product (beginning, middle, and end)
- pH
- Water activity (a_w)
- Tobacco-specific nitrosamine (TSNA) levels
- Preservatives and microbial metabolic inhibitor levels (if any)
- Total aerobic microbial and total yeast and mold count
- An explanation of how the expected storage time (shelf life) is determined
- An explanation of, and rationale for, any differences in the testing procedures and methods used for the new and predicate tobacco products

Consider testing under the storage conditions in which the product is intended to be stored.

D. COMMON DEFICIENCIES – PRODUCT DESIGN ISSUES

1. **Missing design parameter information**
2. **Missing design parameter test data**
3. **Use of interchangeable materials**
4. **Dissolution testing**

1. MISSING DESIGN PARAMETER INFORMATION

Design parameters are foundational information that allows FDA to better understand the tobacco product and fully characterize the new and predicate tobacco products. Comprehensive design parameter information on both the new and predicate tobacco products is important in making an SE determination.

FDA has encountered SE Reports that lack:

- Comprehensive design parameter information
- Range limits for a design parameter

Design parameter specifications may be available in manufacturing data sheets.

- It would be helpful to include any reference documents, such as Certificates of Analysis or Standard Operating Procedures

1. DESIGN PARAMETER INFORMATION

It would facilitate review to provide the target specification and upper and lower range limits for the following types of design parameters for *each* new and predicate tobacco product:

- Product dimensions
  - e.g., length, width, diameter
- Product mass and tobacco mass (if contains tobacco)
- Tobacco moisture content (if contains tobacco)
- Tobacco cut size or particle size (if contains tobacco)
- Characteristics of all papers (if contains paper)
  - Includes paper porosity, bands (if applicable)
  - Applies to pouch paper/material
- Filter ventilation
- Characteristics of the filter (if filtered)

1. DESIGN PARAMETER INFORMATION – COA

A certificate of analysis (COA) from the material supplier may provide adequate design parameter information.

If a manufacturer chooses to provide a COA for a design parameter, it would facilitate FDA review to include:

- Target specification
- Quantitative acceptance criteria (tolerances)
- Units for the parameter
- Test data average value
- Minimum and maximum values of the test data

FDA requests that the COA be a complete, unaltered COA from the material supplier.

2. MISSING DESIGN PARAMETER TEST DATA

In addition to the target specifications and upper and lower range limits, FDA will occasionally need test data confirming that specifications are met. Test data are the measured values of design parameters.

Test data for some critical design parameters are important because the data indicate whether the product can be reproduced consistently according to the intended specifications. A COA from the material supplier may provide adequate design parameter test data.

FDA has encountered SE Reports that:

- Provided COAs that did not include all the information needed to assess the parameter
- Did not explain how nonconforming test data are handled

2. DESIGN PARAMETER TEST DATA

Test data are especially important in cases where:

- There are differences in the target specification between the new and predicate products
- The range limits of the new tobacco product are wider than those of the predicate tobacco product

It would facilitate FDA review if the test data for each parameter provides the following for *each* new and predicate tobacco product:

- Test protocols
- Quantitative acceptance criteria
- Data sets
- A summary of the results for the new and predicate tobacco products
- Data listed on a per unit of measurement of product basis

3. USE OF INTERCHANGEABLE MATERIALS

If a manufacturer selects new or predicate tobacco products that are composed of interchangeable materials, each unique combination is considered a unique tobacco product.

- Any difference in composition (e.g., ingredients, additives, biological organisms) or design parameters (target specifications or range limits) constitutes a new tobacco product
- Distinct new tobacco products may use the same predicate tobacco product for comparison

FDA has encountered SE Reports that provided:

- Unclear descriptions of what information applies to each product submitted in a SE Report

3. USE OF INTERCHANGEABLE MATERIALS

It would facilitate FDA review to provide the following information for *each* tobacco product:

- Every unique material combination
  - Each specific combination of materials will be considered a single new tobacco product and evaluated individually
- A list of ingredients and ingredient quantities for each identified material in each product
- Target specifications and upper and lower range limits for all of the design parameters for each material in each product
- Test data, including test protocols, quantitative acceptance criteria, data sets, and a summary of the results for all of the design parameters for each material in each product

3. USE OF INTERCHANGEABLE MATERIALS

If interchangeable materials are used, options include:

1. Identify a single unique new tobacco product and a single unique predicate tobacco product with a defined set of materials
   - With this option, interchangeable materials will not be reviewed and a SE determination will be made only on the specific new tobacco product identified
2. Identify every unique new and predicate tobacco product that may result from the integration of each combination of interchangeable materials
   - A SE Report is needed for each distinct combination of materials
3. Use a "bracketing" approach to demonstrate that the interchangeable materials do not cause the new tobacco product to raise different questions of public health
   - Compare unique versions of both the new and predicate tobacco products that generate the highest yields of HPHCs with unique versions of the new and predicate tobacco products that generate the lowest yields of HPHCs

4. DISSOLUTION TESTING

Smokeless tobacco products with any of the following changes:

- pH additives
- Target pH changes
- Addition/change binders and fillers
- Tobacco particle size
- Pouch materials

have often received a deficiency related to potential release rate and total nicotine released changes. Changes in nicotine release may affect user perception, user initiation, and use patterns, thus affecting public health. The nicotine release information could be obtained and provided through studies of nicotine in artificial saliva using in-vitro dissolution experiments.

4. DISSOLUTION TESTING

FDA has encountered SE Reports reporting dissolution experiments that lack:

- Dissolution apparatus (apparatus type, media volume)
- Dissolution conditions (e.g., media, temperature, stir/flow rate)
- Dissolution media (e.g., pH, buffers, enzymes, buffer capacity, degassing)
- Description and rationale for the sampling time points
- Description of sample size and disposition (e.g., how much is added to the vessel, was a sinker used)
- Percentage nicotine released relative to a t_{∞} for each sample vs time plots (and data) for a representative sample of the new and predicate tobacco products (t_{∞} is determined by increasing the flow rate for a period of time after steady state is reached)
- Full analytical testing information (Analytical Finish)

E. COMMON DEFICIENCIES – HPHC ANALYSIS ISSUES

1. **Use of modeling to predict HPHC yields**
2. **Addressing toxicity caused by product changes**
3. **Use of quantitative risk assessment (QRA) to address HPHC increases**

1. USE OF MODELING TO PREDICT HPHC YIELDS

FDA has received SE Reports where some data were based on modeling of the design characteristics of the new or predicate tobacco products, but the SE Reports did not provide sufficient evidence to demonstrate the accuracy of the model used.

FDA has encountered SE Reports that lack:

- Critical design characteristics used in the model
- The variables that the model is designed to predict
- The assumptions and rationale for excluding a variable
- The acceptable prediction error for each modelled variable
- The test set used, including the prediction and measured values (Validation)
- A calculation of the predictive error (confidence interval and the prediction interval) for each modelled variable

2. ADDRESSING TOXICITY CAUSED BY PRODUCT CHANGES

When addressing the potential effects of product changes, it is helpful for the manufacturer to account for the potential toxicity of any changed ingredients via the route of exposure (e.g., inhalation), and the effect of changes to the product upon HPHC delivery (e.g., combustion of an ingredient to form a HPHC).

Some approaches to address toxicity of product changes include:

1. Submitting data showing that there are no increases in HPHC delivery
2. In vitro studies to address the human cancer risk and non-cancer hazards due to the HPHC increases
   - It would facilitate review to include a rationale for how the studies address the expected human cancer risk/non-cancer hazards
   - Such studies may potentially address concerns about the human health effects of ingredients in their unchanged form

2. ADDRESSING TOXICITY CAUSED BY PRODUCT CHANGES

Some approaches to address toxicity of product changes include:

3. Toxicological analyses of ingredients or HPHCs that have been or can be used to establish health protective reference values applicable to anticipated human exposures from use of the new tobacco product and how the reference values address the toxicological effects expected from the new tobacco 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 toxicological practice to assume a linear relationship between the dose of a carcinogen and an increased risk of cancer
   - An ingredient's generally recognized as safe (GRAS) status has not been evaluated for inhalational exposure and are dose dependent

2. ADDRESSING TOXICITY CAUSED BY PRODUCT CHANGES

In these toxicity analyses, it is important to consider the following parameters:

- Route of administration
- Relevance of animal species tested; species strain- and sex-specific effects
- Dose-response profile
- Exposure frequency and duration
- Adverse or critical effect identifiers (e.g., lowest observable adverse effect level (LOAEL))
- Adjustment of the critical effect level to the dose metric of interest
- Biological significance of response
- Interpretation of results and relevance of uncertainty factors used
- Availability of supporting evidence (e.g., structure-activity relationships) and relevance of results to humans
- Available information on the metabolic fate and disposition of ingredients

3. USE OF QRA TO ADDRESS HPHC INCREASES

- HPHC comparisons are an important aspect of the toxicity evaluation between new and predicate products in SE Reports
- It is important to note whether the HPHC increases have any offsetting HPHC decreases
- The quantitative risk assessment (QRA) approach may only be useful in addressing HPHC increases in specific situations where there are both HPHC increases and decreases
- QRAs – by themselves – cannot address HPHC increases and are not useful if:
  - There are no HPHC decreases that could possibly offset HPHC increases
  - There are only HPHC decreases and no HPHC increases
  - HPHC measurements used are not statistically and analytically different from predicate product values (e.g. based on analytical method limitations)

3. USE OF QRA TO ADDRESS HPHC INCREASES

- Consider a qualitative analysis before embarking on a quantitative approach
- Such an analysis can help determine whether:
  - A quantitative approach would be useful
  - A quantitative approach is unnecessary
- It is critical that a qualitative analysis focus on *statistically and analytically different* HPHC measurements

3. USE OF QRA TO ADDRESS HPHC INCREASES

If a QRA is submitted, it would facilitate FDA review to include the following:

1. The specific question(s) addressed by the QRA and clearly define the overall risk model
2. 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 of the National Academies (2009)
3. All raw data, equations, assumptions, parameters, outputs, and references used
4. Justification that the QRA is appropriate for comparing the relative human health risks and hazards from use of the new and predicate tobacco products for the relevant user population

3. USE OF QRA TO ADDRESS HPHC INCREASES

If a QRA is submitted, it would facilitate FDA review to include the following:

5. 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
6. Evidence that the constituents considered in the composite QRA are representative of potential differences in the cumulative hazard and risk of the tobacco products
7. Evidence that the evaluation can discern a difference in hazard and risk between the new and predicate tobacco products

SUMMARY

- SE Report overview
- Common deficiencies
  - Predicate tobacco product issues
  - Ingredient review issues
  - Constituent reporting issues
  - Product design review issues
  - HPHC and Toxicological analysis

THE END