

PMTA: Product Characterization

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Product Identification

- Design Specifications
- Ingredients
- Harmful and Potentially Harmful Constituents (HPHCs)
- Product Stability

Design Specifications

The PMTA must provide as outlined in 21 CFR 1114.7(i)(2)(ii):

A listing of the design components and specifications in the new product in a table including:

- Identification of the components/parts and materials that comprise the new product (e.g., batteries, heating element).
- Target design specifications with the upper and lower range limits of each component.
- Measured values (test data) to demonstrate that the design specifications are met throughout the manufacturing process.

Product Name	Component	Design Parameter	Unit	Specification			Test Data (Y/N)	Test Protocol No.	Measured Values		Within Specification (Y/N)
				Target Value	Min.	Max.			Min.	Max.	

Ingredients

The PMTA must provide as outlined in 21 CFR 1114.7(i)(1)(iii):

A listing of all single and complex ingredients in the new product in a table including:

- Ingredient name (IUPAC or common), chemical abstracts service (CAS) number, purity/grade and supplier, and function(s).
- Component that the ingredient is found in the new product (e.g., e-liquid).
- Target quantity and range for each ingredient, with the unit of measure (e.g., mg/mL or mg/unit).

Product Name	Component	Function	Complex Ingredient (if applicable)	Ingredient Name	IUPAC Name	CAS Number/ FDA UNII	Manufacturer	Purity/Grade	Unit	Target Quantity	Range	
											Min.	Max.

- For complex ingredients – provide each single chemical substance reported separately including the information noted above that comprise the complex ingredient.
 - Using tobacco product master files for complex ingredients such as flavor formulations is an avenue to providing this information to FDA.

Ingredients – Nicotine Source

The PMTA must provide information about the source of nicotine [See Form FDA 4057b and 21 CFR 1114.7(i)(1)(iii)]. It is helpful to provide this information in a table, including:

- Component that the ingredient is found in the new product (e.g., e-liquid)
- Nicotine form (e.g., salt)
- Nicotine form name (e.g., nicotine lactate)
- Nicotine source (tobacco and/or non-tobacco nicotine [NTN])
- Enantiomeric purity (for NTN only, e.g., percent S or R)
- Purity/grade (e.g., USP)
- Target quantity and range for each ingredient, with unit of measure (e.g., mg/mL)

Product Name	Component	Nicotine Form (e.g., unprotonated, salt, complex)	Nicotine Form Name (e.g., nicotine lactate, nicotine polacrilex)	Nicotine Source (e.g., TDN, NTN)	Enantiomeric Purity	Purity/Grade (e.g., USP)	Unit	Target Quantity	Range	
									Min.	Max.

Harmful and Potentially Harmful Constituents (HPHCs)

The PMTA must provide as outlined in 21 CFR 1114.7(i)(1)(v):

A listing of the measured HPHCs in the new product in a table including:

- Constituent name, mean, number of replicates, standard deviation, and unit of measure.
- Type of emission regimen used and/or cited standard, if applicable.

Product Name	Constituent	Regimen (if applicable)	Unit	New Product			Comparison Product(s)			% Change
				Mean	SD	N	Mean	SD	N	

Comparison products for ENDS for HPHC comparisons to the new product could include cigarettes and other FDA authorized ENDS products on the market.

- HPHC yields between the new product and to comparison products on the marketplace is crucial in weighing the evidence for an APPH decision.

Microbial and Product Stability

The PMTA must provide as outlined in 21 CFR 1114.7(i)(1)(vii):
Microbial stability data for the new product in a table including:

- Water activity
 - Total aerobic microbial count (TAMC)
 - Total yeast and mold count (TYMC)
 - NNN, NNK, and total TSNA
- Measurements should be taken at the beginning, middle, and end of the proposed shelf life of the product.

Product Name	Storage Time [Units]	Water Activity (a _w)	TAMC ([UNITS])	TYMC ([UNITS])	β-glucan (if applicable) ([UNITS])	Endotoxin (if applicable) ([UNITS])	NNN ([UNITS])	NNK ([UNITS])	Total TSNA ([UNITS])
	[Beginning]								
	[Middle]								
	[End]								

- For e-liquids, we also suggest β-glucan and endotoxin testing.

Other Product Identification Considerations

- Chemical and microbial testing procedures
- Leachables and extractables studies for ENDS components and container closure system materials
- Information needed to support product bridging

Method Validation for HPHCS and Microbial Analysis

- Process of demonstrating or confirming that the chemical or microbial test method is suitable for its intended purpose.
- Validation procedures are conducted relative to a reference product similar to the product that is tested.
- Analytical method validation considers the entire analytical method, including analytical procedure, controls, and sampling procedure.
 - Accuracy
 - Precision
 - Selectivity
 - Sensitivity

Method Validation Parameters

- Accuracy - the closeness of mean test results obtained by the analytical method to the true value of the analyte.
- Precision - closeness of individual measurements of an analyte when the procedure is applied repeatedly to multiple aliquots of a single, homogenous solution of an analyte.
- Selectivity - the ability of an analytical method to differentiate and quantify the analyte of interest in the presence of other matrix components present in the sample.
- Sensitivity - the limit of quantification and the limit of detection.

Verification Process

- A validated method can be extended to other products within the same category through a verification process.
- Verification is the demonstration of a laboratory's ability to successfully meet performance criteria established for an analytical test method previously validated in the laboratory performing the validation.
- Any substantial changes to a method result in a new method should be independently validated.

Common Issues Seen with Methods

- Deviations to standardized methods are not reported or explained
 - Inappropriate reference standard used for method development
 - Inadequate number of replicates analyzed
 - Method has not been demonstrated to be validated for the product type (i.e., matrix) under review
 - Validation reports not provided
 - Limit of quantitation not reported
 - Lack of appropriate or any controls for microbial test methods
- FDA recommends the use of the Validation and Verification of Analytical Testing Methods Used for Tobacco Products Guidance finalized in January 2025

Leachables – ENDS Components and Container Closure Systems

- FDA is concerned with constituents that may leach from the components in direct contact with the e-liquid that then may transfer into the aerosol inhaled by users.
 - The potential for leachables and their harm is less well understood for ENDS components and parts contained in an organic e-liquid (as compared with mostly aqueous medical products), thus the need for product-specific extraction and leachable studies.
- Materials in container closure systems can produce potentially hazardous constituents (e.g., certain plastics can release antimony), which is why leachable studies on the container closure system may also be needed.
- Reporting exact quantities for any leachables observed above pre-established thresholds (e.g., analytical evaluation threshold) and evaluate their potential risks to users is helpful to FDA.

Extractables - ENDS Components and Container Closure Systems

- Extractable studies performed in the design phase on individual components and parts in direct contact with the e-liquid can help applicants avoid containers, coils, seals, etc. that may leach potentially harmful constituents into e-liquids in their finished product.
- Extractables studies and non-targeted analysis help target and identify constituents from leachables studies that often have more complicated data (e.g., more interferences).
- Constituent identification can be challenging - explain to the best of your ability how you arrived at your identification.
- Confirming the identification of every constituent may be quite challenging, however, provide as much identifying information as possible and how each constituent may impact the risks of using the product.

Product Characterization: Data and Rationale for Bridging

- Provide appropriate scientific rationale to justify why the study findings apply to the new tobacco product and any study limitations that may be relevant.
- Bridged products should be representative and measured using the same conditions that the new or comparator products are expected to be in (e.g., same shelf life, same container closure system).
- Some possible examples where bridging may be possible for product characterization:
 - HPHCs could be used for a similar product (e.g., prototype product) if that product can be demonstrated to be similar to the new product.
 - Design specifications of the components of the products could be bridged but ideally an applicant is providing the design specifications of the components that are expected to be used in the new product.

Essential Takeaways

- FDA needs complete product identifying information such as ingredients, HPHCs, design specifications, and shelf-life of the product to understand the physical properties of the product.
- Understanding the basic characteristics of the product is the first crucial step for FDA in its decision making to determine if a product is appropriate for the protection of public health.
- All test methods are expected to be validated and/or verified on the product type intended to be authorized.
- Tobacco product master files (TPMFs) are useful for product characterization especially for complex ingredients that are proprietary (e.g., flavor formulations) and validation/verification procedures for analytical and microbial test methods.
- Tell your story to FDA about your product so we understand the complete physical characterization and composition/design of your product.

Helpful Resources

- Guidance for Industry: [Listing of Ingredients in Tobacco Products](#), updated March 2023
- Guidance for Industry: [Premarket Tobacco Product Applications for Electronic Nicotine Delivery Systems \(ENDS\)](#), updated March 2023
- Guidance: [Validation and Verification of Analytical Testing Methods Used for Tobacco Products](#), January 2025
- Premarket Applications: Opportunities for Stakeholder Engagement - A Public Meeting; [Extractables and Leachables Evaluation](#), October 2023
- Posted FDA Memos: [Approaches to the Evaluation of Extractables and Leachables in Tobacco Product Application Review](#)

PMTA: Product Manufacturing

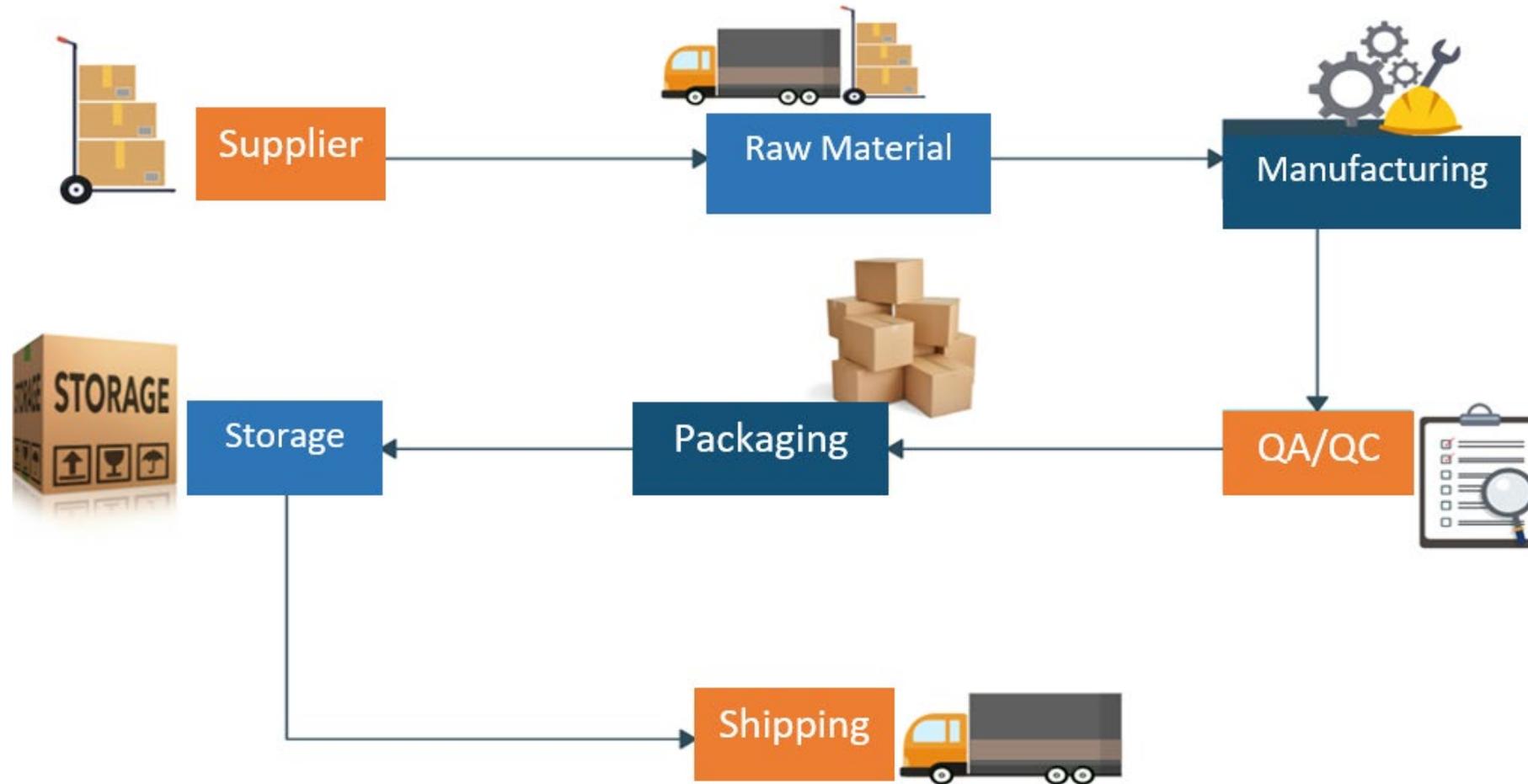
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Overview of manufacturing process



Manufacturing Workflow Template by Creately Templates, found in: [Manufacturing Workflow Template | Creately](#)

Quality Management System (QMS):

- Can be based on standards such as ISO 9001
- Establish and document comprehensive quality procedures:
 - Incoming inspection
 - In-process controls
 - Finished product testing
 - Non-conformance handling
 - Corrective actions
 - Document control
- Approach should consider both quality assurance (QA) and quality control (QC) aspects
 - QA is process-oriented and focuses on defect prevention
 - QC is product-oriented and focuses on defect detection

Critical Manufacturing Documentation:

- Standard Operating Procedures (SOPs):
 - Should cover all critical manufacturing operations (who, what, and when)
- Work Instructions (WIs):
 - Detailed step-by-step instructions on task completion (how)
- Certificate of Analysis (COA):
 - Demonstrate consistent manufacturing within established steps including from your suppliers
- Batch Records:
 - Complete production and control documentation for each batch (who, what, when, and how)

Product Consistency and Manufacturing Control

Key Considerations:

- Demonstration of product consistency through standard operating procedures, work instructions, certificates of analysis, and batch records
- Manufacturing specifications that align with labels/labeling for nicotine
- Information to support that products are chemically and microbiologically stable
- Information to support intended function of all features that mitigate risks associated with the new product

Common Issues with Manufacturing Process Descriptions

- Incomplete manufacturing process descriptions and procedures
 - Lack of SOPs or WIs (e.g., nonconformance handling, training)
 - Lack of examples of relevant forms and records
- Inadequate quality control
 - Missing functional testing
 - Missing sufficient performance verification
- Incomplete information about manufacturing steps
 - Source of components is unclear
 - Missing information about acceptance of materials
 - Assembly steps are not fully described

Common Issues with QMS Documents

- SOPs lack sufficient detail or are unclear
- WIs do not include acceptance criteria for in-process checks
- COAs are missing:
 - target specification with units
 - quantitative acceptance criteria with units
 - test data average
 - either standard deviation or minimum and maximum values
- Incomplete information in batch records (e.g., missing steps or in-process test results)

Manufacturing Specifications for Nicotine

- Provide target nicotine quantity specifications, upper and lower range limits, and acceptance criteria for the finished products
- Include in-process checks to ensure nicotine quantity is within specifications at each step
- Demonstrate the target specifications, acceptance criteria, and labels/labeling claims are met with your manufacturing information (e.g., batch release data)

If Nicotine Quantity is Not Well-Controlled:

- Consumers will not receive a consistent product and may use the product more frequently
- If consumer use varies, exposure to harmful and potentially harmful constituents (HPHC) may be higher than anticipated
- Abuse liability may be impacted – an increased quantity of nicotine may be more addictive
- We won't know if the products used for abuse liability and other clinical or behavioral studies are representative of real-world use

Why Stability Studies Matter

- Demonstrates that the product remains consistent throughout its shelf life
- Demonstrates that key product characteristics (e.g., nicotine quantity, water activity, pH) remain within acceptable ranges over time
- Products may undergo chemical or microbial changes that create new harmful and potentially harmful constituents or increase existing ones, which could impact public health
- Ensures consumers use a consistent product and aren't exposed to degradation products or microbial contamination (e.g., endotoxins in e-liquids that could be harmful if inhaled)

Information to Support Stability Studies

- Ensure stability studies reflect the product shelf life
- Stability studies must use at least three timepoints (i.e., beginning, middle, and end of shelf life)
- If the stability study does not support the shelf life specified, the product may receive a marketing granted order for the shelf life that the stability study supports
- Conduct testing at intended storage conditions
- Accelerated studies are not appropriate for microbial stability studies

Additional Information on Stability Studies

- If testing is conducted by a third-party laboratory that uses a tobacco product master file (TPMF), ensure a letter of authorization to use the TPMF is provided in your application.
- Stability studies should use validated methods. Validation data and test methods should be provided.
- Data from unvalidated test methods do not provide confidence that the data is accurate, repeatable, and representative of the finished product.

Risk Analysis

- Failure mode and effects analysis (FMEA) or other risk analysis
- Identify design and process risks and mitigations
- Verify that no additional risks were added during manufacturing stages
 - If they were – include evidence of mitigation (e.g., a process FMEA (pFMEA))
- Mitigation of product design and process risks are associated with protection of public health

Some Common Features that Mitigate Risk

- Maximum puff duration limits - may prevent overheating and excessive exposure to nicotine and other HPHCs
- Time-out functions – automatic shutoff after specified use period
- Temperature controls – mitigates excessive heating
- Low-voltage cutoff – protects the battery
- Child-resistant packaging – mitigates accidental exposure

Risk Mitigation Testing

- Consider how each feature (e.g., maximum puff duration) affects the constituents emitted from your products
- Confirm that features operate as intended under normal conditions
- Test the product under abnormal and misuse conditions
- Explain how features are tested and measured (and if the tests comply with industry standards (e.g., ISO or UL))
- Report adverse experiences and explain how they are documented and resolved

Risk Mitigation for ENDS

Consider and test the whole system

- Device
- Cells/batteries
- Power supplies
- Protective circuits and controls

Devices

- Construction and materials
- Vent away from user
- Test with the cell/battery

Cells & batteries

- Consider industry standards (e.g., UL 1642)
- Inaccessible cells
- Integrated or device-specific

Power supplies

- Universal or device-specific
- Consider industry standards

Key Takeaways:

- Provide complete manufacturing process information (e.g., SOPs, WIs) to cover all processing steps from sample receipt to shipping of the finished products
- Demonstrate that nicotine quantity in the finished product meets specifications
- Conduct sufficient chemical and microbial stability studies to demonstrate product integrity over shelf life
- Provide information to support intended function of all features that mitigate risks associated with the new product

Pharmacological Profile

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Outline

- Abuse liability
- Pharmacokinetic Study Design
- Study Population
- Product Bridging

Abuse Liability

- Abuse liability refers to the potential of a substance to result in addiction and be used repeatedly or even sporadically resulting in undesirable effects. (PMTA Rule)
- Addiction is a chronic, relapsing disorder characterized by compulsive drug seeking and use despite adverse consequences. (National Institute of Drug Abuse [NIDA])
- The abuse liability of a new tobacco product is important for FDA to evaluate because it indicates the degree to which users of the tobacco product are likely to use and develop an addiction to the product. “Abuse liability may result in craving of the product and compulsive and continued use despite harm or risk of harm” (PMTA Rule) and may also indicate the likelihood of product switching.

Nicotine and Pharmacokinetic Study Design

- Nicotine is the primary addictive substance in tobacco products, and the rate, degree, and total amount of nicotine delivery into the brain significantly impacts product abuse liability.
- Behavioral and Clinical Pharmacology (BCP) assesses abuse liability based on totality of evidence, with clinical studies providing the strongest evidence. A clinical study measuring nicotine pharmacokinetic outcomes give us data to directly evaluate nicotine exposure.
- The most common clinical study design to support a new product specific abuse liability evaluation is a multi-session, randomized, crossover study comparing the pharmacokinetic (PK) profiles of several new products to comparison products with a known abuse liability (e.g., combusted cigarettes).

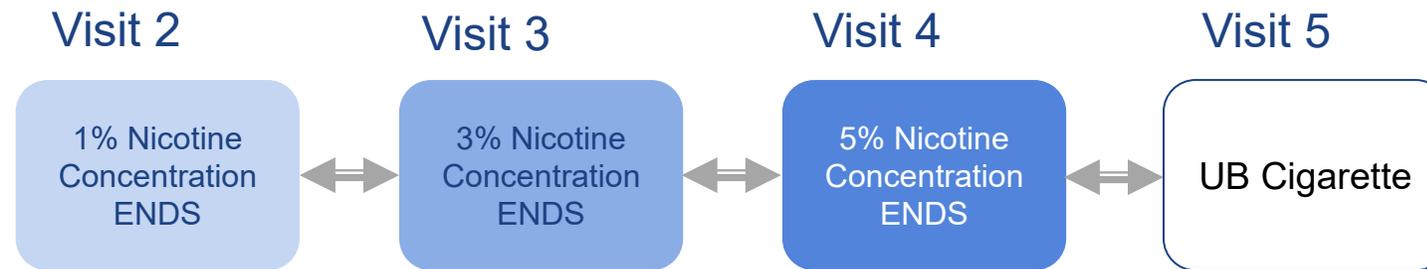
Hypothetical Study Design

* This hypothetical study design will be referenced later in hypothetical product bridging examples

Visit 1: Screening, Participant Consent, and Randomization

Laboratory Visit:

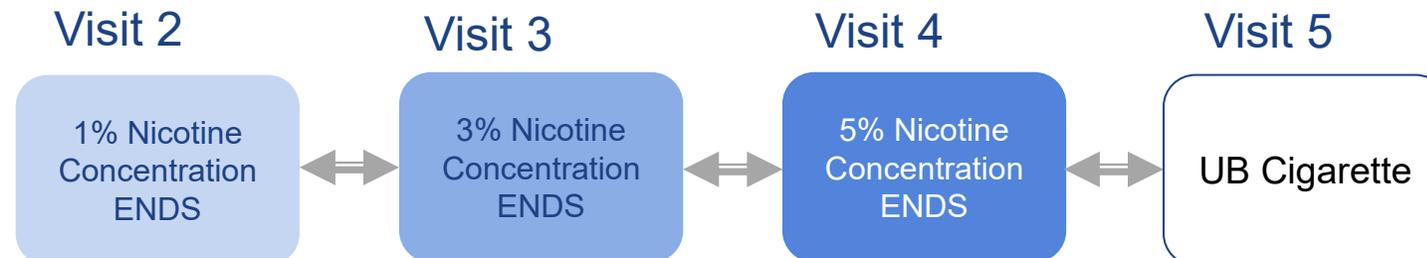
**Phase A
Prescribed Use**



(Outcome measures: Nicotine Pharmacokinetics and subjective effects)

Laboratory Visit:

**Phase B
Ad Libitum Use**

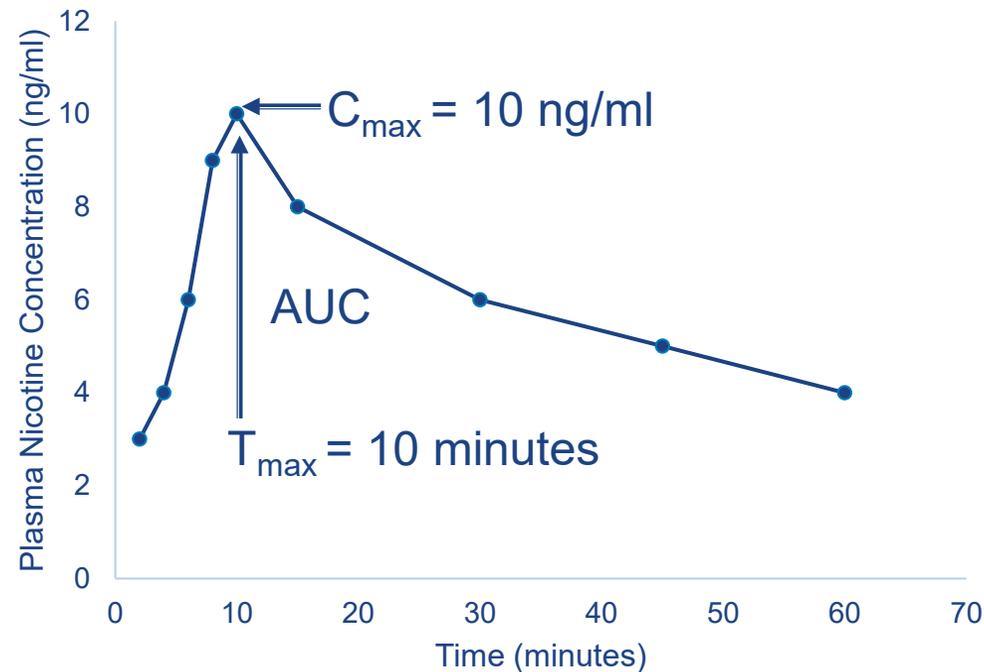


(Outcome Measures: Nicotine Pharmacokinetics, puff topography, and subjective effects)

Abuse Liability Study Outcome Measures

- Nicotine Exposure

- Acute exposure: Nicotine pharmacokinetics (PK) including C_{max} , T_{max} , $AUC_{(0-t)}$
- Chronic exposure: Total Nicotine Equivalents (TNE) in blood or urine



Abuse Liability Study Outcome Measures

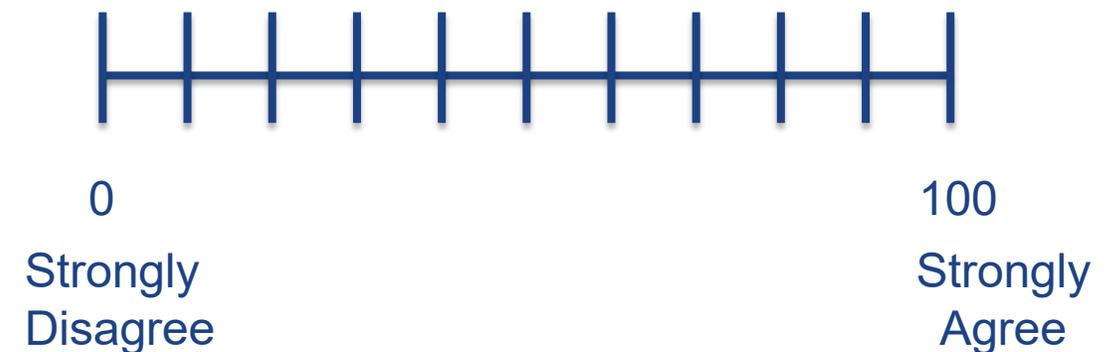
- Nicotine Exposure

- Acute exposure: Nicotine pharmacokinetics (PK) including C_{max} , T_{max} , $AUC_{(0-t)}$
- Chronic exposure: Total Nicotine Equivalents (TNE) in blood or urine

- Subjective measures

- e.g., drug liking, satisfaction, craving, withdrawal

I have a desire for a cigarette right now.



Abuse Liability Study Outcome Measures

- Nicotine Exposure
 - Acute exposure: Nicotine pharmacokinetics (PK) including C_{max} , T_{max} , $AUC_{(0-t)}$
 - Chronic exposure: Total Nicotine Equivalents (TNE) in blood or urine
- Subjective measures
 - e.g., drug liking, satisfaction, craving, withdrawal
- Use topography
 - e.g., number of puffs, puff volume, and duration

Study Population

- Applicants typically include adult users of either the category of new product (e.g., ENDS) and/or regular adult users of the comparison product (e.g., combusted cigarettes).
- Consider both the intended user population and the likely user population
- Prior experience with the study product or product category may affect interpretation of study outcomes and impact study confidence.
 - Experienced ENDS users can achieve higher nicotine exposure from the same ENDS compared to ENDS-inexperienced cigarette smokers.
- Justify the selected participant population

Other Considerations

- Comparison product selection
- Study quality and confidence
 - For example, insufficient sample size could decrease the quality of the study
 - The quality of the study will contribute to the confidence in the outcome measures and how the outcome data will be weighed in totality of evidence when evaluating abuse liability

Product-Specific Information

- The abuse liability of a new ENDS is influenced by the combination of device and e-liquid characteristics.
- Product-specific information (i.e., data from an abuse liability study using the new product) serves as the strongest source of information for an abuse liability determination of the new products.
- When product specific information is not available, applicants may attempt to bridge the new product to data from studied products.

Bridging

Bridging is a tool to utilize existing evidence to inform review of a new product lacking data

- Bridging requires:
 - Identification of product differences
 - Evidence based rationale
- If bridging is inappropriate
 - Those data will not be considered in the review

Bridging

- Ideally, the applicant-submitted studies will include all the new products subject to review in the application.
- However, when the submitted evidence does not include all the new products (i.e., a subset of the new products) or evaluates products not subject to the PMTA (e.g., study products with any differences compared to the new product, including precursor versions of the new product or different flavors, that are tested in a clinical study), applicants may bridge data generated from the study product(s) to support an abuse liability evaluation of each of the new products.
- When bridging to new products, bridging information should include details and scientific discussion on whether and to what extent the differences between new and study products affect abuse liability measures (e.g., nicotine pharmacokinetics and exposure, subjective effects, use behavior) and scientific rationale for how the results of the study products are applicable to the new products.

Product Bridging

BCP assesses applicant's bridging for:

- Differences in product characteristics (e.g., nicotine concentration, device power)
- Evidence based rationale on whether, and by how much, product differences affect abuse liability measures (e.g., nicotine PK, subjective effects, use behavior)
- Whether the differences might support a different abuse liability for the new product versus the study product
- Many of these evaluations are conducted in conjunction with other disciplines, like chemistry and engineering.

Product Characteristics

- Product characteristics known to influence abuse liability outcomes include (but not limited to):
 - Nicotine concentration and formulation (freebase, salts)
 - Product flavor
 - Device type and power (ENDS)
 - PG/VG ratio (ENDS)
 - Free nicotine content (nicotine pouch)
- Consider individual product characteristics and the combination of total product characteristics of the new and study products in determining the appropriateness of product bridging. The more product characteristics that differ between new and study products, the more difficult and complex it becomes to appropriately bridge the products.

Data That Can Support Bridging

- Clinical studies provide the most useful bridging information
 - Nicotine PK studies
 - Use behavior studies
- Non-clinical data can be useful, such as:
 - Machine-generated aerosol data
 - Ingredient homology
- Published literature may be acceptable when:
 - Explicit rationale and justification as to why the products used in a published study can be bridged to the new products, considering the many characteristics that influence abuse liability.

Bridging Hypothetical: Nicotine Concentrations

- The level of nicotine in a tobacco product may affect how the product is used (e.g., use topography) and therefore may influence dependence and HPHC exposure.
- To appropriately bridge from a subset of tested new products to untested new products, evidence based scientific rationale demonstrating that the outcome measures obtained from the tested subset is also representative of the untested subset.
- For example, the experimental design could include low, medium, and high nicotine concentrations representative of the new product line.

Tested New Products



Untested New Products



* Using the hypothetical study design described earlier

Bridging Hypothetical: Characterizing Flavor

- Consider how the various flavors and flavor constituents in the new products may impact use behavior, and thus may influence user's exposure to nicotine.
- Consider the possibility that subjective measures of abuse liability may differ for each new product, including those that will be tested in the clinical studies and those that will not be tested.

Tested New Products

Tobacco
Flavored
ENDS

Menthol
Flavored
ENDS

Strawberry
Flavored
ENDS



Untested New Products

Mint Flavored
ENDS

Blueberry
Flavored
ENDS

* Using the hypothetical study design described earlier

Abuse Liability Summary

- Abuse liability information indicates the likelihood of users to become addicted to the product.
- Applicants should design abuse liability studies with consideration of comparison products, the intended and the likely user populations, and methodological constraints.
- Applicants should provide explicit, product specific, justification to support bridging for any untested new products that are not evaluated in a study.
- Abuse liability evaluations are based on the totality of abuse liability information, with clinical studies providing the strongest evidence.
- Ultimately abuse liability is one puzzle piece in a broader APPH evaluation that takes into account all scientific disciplines.

Evaluating Evidence of Adult Benefit for Flavored ENDS PMTAs

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AGENDA

- Relevant background on PMTAs and potential adult benefits of flavored ENDS
- Design considerations for randomized controlled trials, cohort studies, and actual use studies

Review of ENDS PMTAs

- FDA assesses the scientific evidence to determine if the marketing of the new tobacco product is appropriate for the protection of the public health
- FDA assesses the applicant's scientific evidence to evaluate the risks and benefits to the population as a whole, including:
 - Likely users and nonusers of the new product under review
 - Whether people who currently use any tobacco product would stop
 - Whether nonusers would start
- The evaluation of behavioral evidence of adult benefit is one aspect of PMTA review that, along with findings from other review disciplines, is integrated by the TPL in overall APPH decision-making.

Youth Considerations

- Preventing youth use is a key consideration
- The risks to youth posed by flavored ENDS are substantial and well-established
- FDA has concluded that flavored ENDS present significant risk to youth with respect to appeal, uptake, and use
- Nearly 90% of youth who use ENDS report using a flavored product—with fruit being the most reported flavor type overall, by school level, and across all e-cigarette devices

Source: Park-Lee et al. MMWR. 2024; Rostron et al. Am J Health Behav. 2020; Audrain-McGovern et al. Drug Alcohol Depend. 2019; 2016 Surgeon General's Report

Adult Benefit

- A growing body of evidence suggests that ENDS may facilitate transitions away from combusted cigarettes
 - 2025 Cochrane Review concludes: There is high-certainty evidence that electronic cigarettes with nicotine increase quit rates compared to nicotine replacement therapy (NRT)
- However, while flavored ENDS are known to be appealing to and widely used by adult smokers, there is limited data and mixed findings about the benefits of flavored ENDS, as a category, for switching and cessation.

Source: Lindson et al. Cochrane Database Syst. Rev. 2025

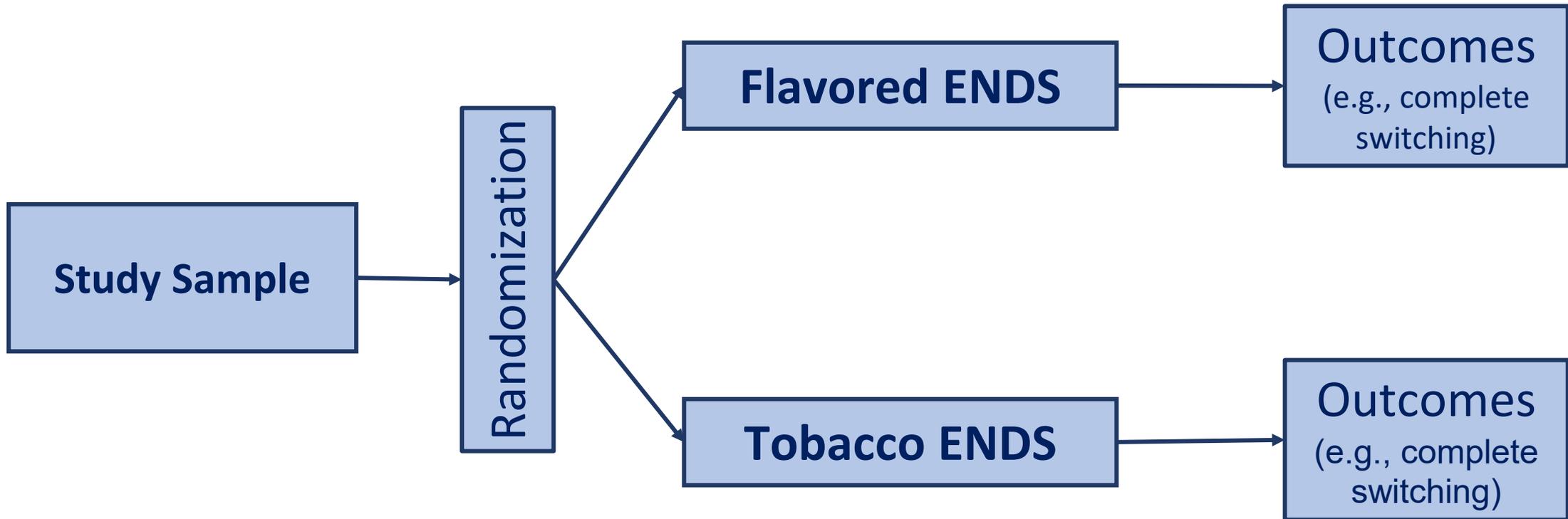
Added Benefit of Flavored ENDS

- In reviewing PMTAs for flavored ENDS, FDA looks for sufficiently robust and reliable product-specific evidence demonstrating the flavored ENDS have an added benefit for adult smokers relative to that of tobacco-flavored ENDS in facilitating adults who use combusted cigarettes in completely switching from or significantly reducing their smoking.
- This evidence of added benefit is needed to outweigh the well-established risks of flavored ENDS products to youth & young adults
- By contrast, tobacco-flavored ENDS are associated with a lower risk of youth use and appeal. Therefore, the strength of evidence and magnitude of benefits to adult smokers that is needed in the application is relatively lower and may be derived from other data sources

PMTA Review of Flavored ENDS (FE)

- Two types of product-specific evidence most likely able to demonstrate this added benefit to adult smokers:
 - Experimental evidence: randomized controlled trials (RCTs)
 - Observational evidence: cohort studies or actual use studies
- Other types of reliable and robust evidence may also demonstrate this added benefit to adult smokers
- When present, such information will be substantively evaluated to determine if the potential benefit outweighs the significant known risk to youth such that marketing the product would be APPH.

Randomized Controlled Clinical Trial (RCT) Design Considerations

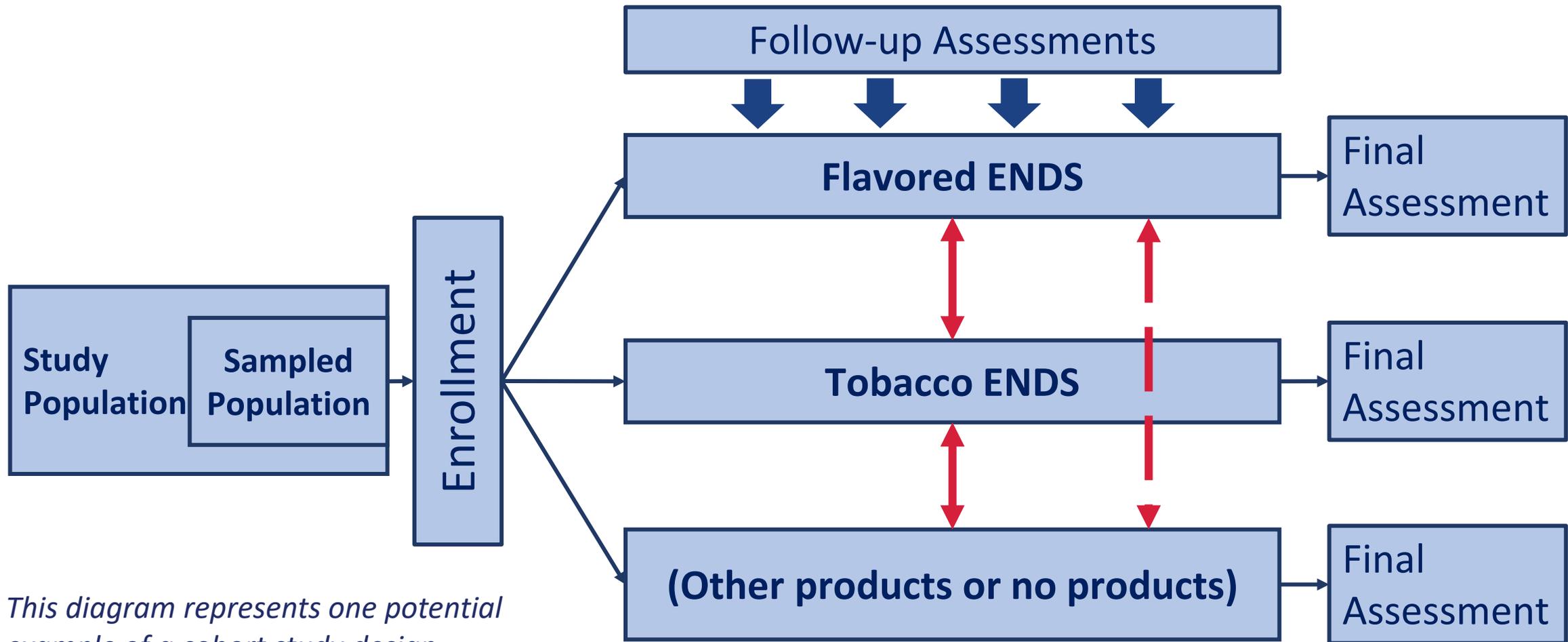


This diagram represents one potential example of an RCT design.

RCT Considerations: Randomization

- Study design and conditions may vary across applications
 - FDA reviews scientific rationale for study design, randomization procedure
- General experimental conditions for flavored ENDS RCT
 - Randomized to a specific flavored product
 - Randomized to a flavored ENDS arm; participant chooses preferred flavored product

Cohort Study Design Considerations



This diagram represents one potential example of a cohort study design.

Study Considerations: Exposure

- In RCT, cohort, and actual use study designs, the exposure should be the new flavored ENDS product(s)
- FDA reviews flavored ENDS' switching outcomes as compared to a tobacco-flavored comparison ENDS' outcomes
 - All comparison ENDS should be appropriate given the flavored ENDS under review
- Evaluating the tobacco-flavored comparison product in the same study as flavored ENDS will enable the most valid comparisons

Study Considerations: Duration

- FDA looks for study durations to be appropriate for outcomes measured and scientifically justified in the study protocol
 - Although 6 months is a standard study duration for smoking cessation trials¹, studies shorter than six months may also inform an assessment of the added benefit of a flavored ENDS product.
 - Demonstrations of complete switching to a flavored ENDS product for periods shorter than 4 weeks may not be sufficient to provide robust evidence of behavior change
- Loss to follow-up and missingness can be a substantial limitation in longer term studies; FDA evaluates approaches to handle missing data (e.g. multiple imputation; coding “missing-as-smoking”)

¹West R, et al. (2005). Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction*, 100(3), 299–303.

Study Considerations: Outcomes

- Complete switching as a primary outcome
 - Typically, complete cigarette abstinence (past 7-day or past 30-day), may be self-report or biochemical validation¹
 - Longer duration (e.g., 6-to-12-month) studies can consider a maximum allowable number of cigarettes
 - Combined complete switching and cessation of all tobacco products may also be reported as a secondary outcome (i.e., using neither CC nor ENDS)
- Additional outcomes
 - Significant CPD reduction, nicotine withdrawal, 7-day point prevalence

¹West R, et al. (2005). Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction*,100(3),299–303

Considerations for Actual Use Studies

- In addition to cohort studies, actual use studies are an example of an observational study design
- Whereas cohort study participants purchase their own products, actual use study participants select from a subset of products the investigator presents as options
- Actual use studies may be more appropriate in cases where the new products are not currently marketed
- With this difference in mind, considerations and evaluation of cohort studies can be applied to actual use studies as well

Additional Considerations: Bridging

- Ideally, the RCT or cohort studies will include all the new products subject to review in the application
- In some cases, evidence on each individual flavor option or nicotine concentration may not be feasible; for instance, bridging data from one of the applicant's flavors to another flavor (e.g., within the same flavor category) may be appropriate
- FDA's bridging evaluation focuses on whether, and to what extent, differences between new and bridged study products may affect adult switching
- Applicants should provide data and explicit justification to support bridging (e.g., abuse liability data)

Product Toxicological Hazard is Something ENDS Manufacturers Can Control

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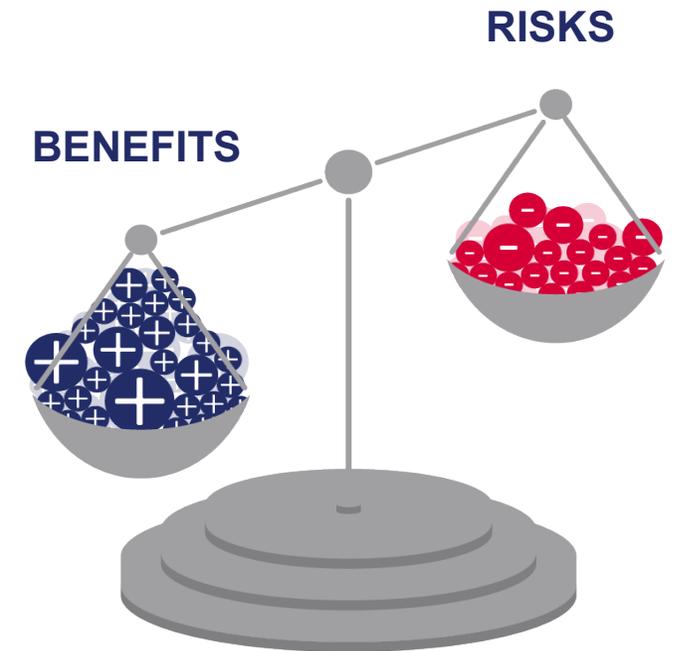
Agenda

- How does risk assessment fit into PMTA?
- Toxicological Profile – Cancer and Noncancer
- Discussing CTP’s new regulatory science policy memos:
 - June 03, 2024: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications
 - June 03, 2024: Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications
 - July 08, 2025: Addendum to June 3, 2024, Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications Memorandum
- Product Design is Key
- Generic examples of how ELCR could be reduced
- Conclusions

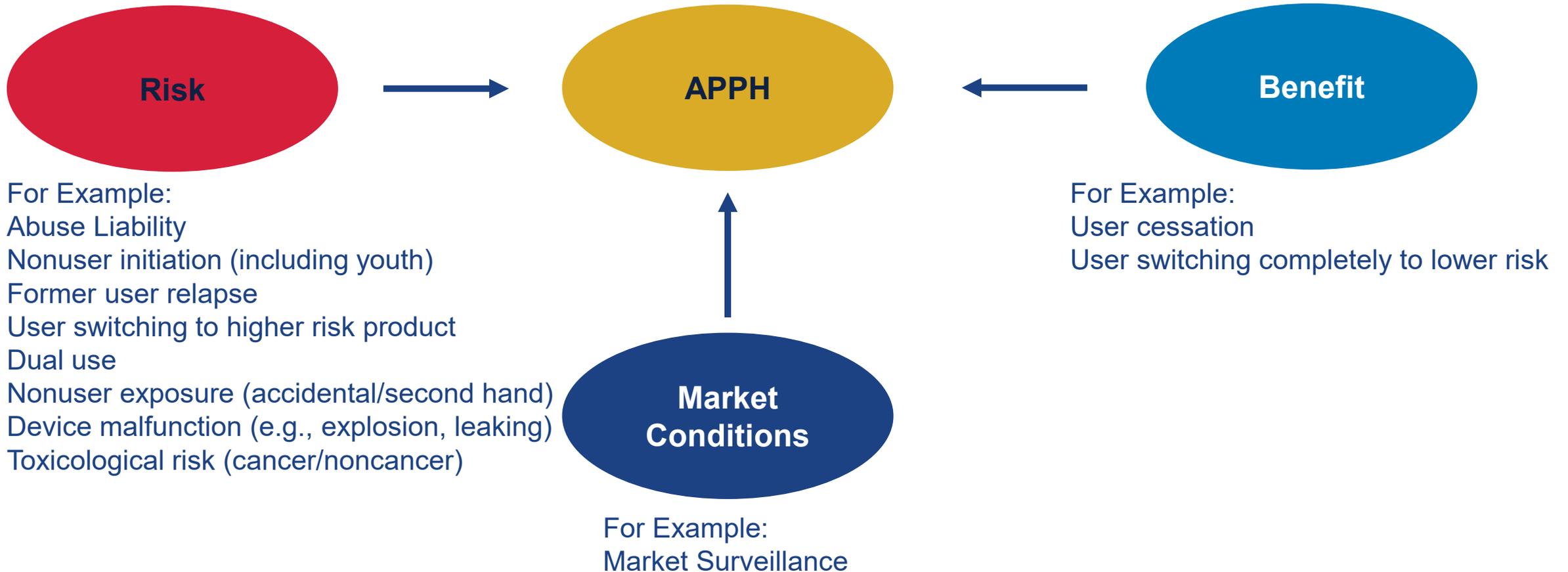
PMTA and APPH: Where Does Risk Assessment Fit?

Review of PMTA and APPH

- PMTA program can impact public health by proactively shaping a regulated marketplace that is characterized primarily by nicotine-containing tobacco products towards the lower end of the continuum of risk.
- CTP's task is to assess the applicant's scientific evidence to determine if the marketing of the tobacco product is appropriate for the protection of the public health.
- To do this, we must assess the risks and benefits to the population as a whole, including users and nonusers of the tobacco product.



Components of APPH



Components of APPH



Toxicological risk

Cancer

- Genetic toxicity
- Carcinogenicity studies

Non-cancer (Health Outcome Domains)

- Respiratory toxicity
- Developmental and Reproductive Toxicity
- Cardiotoxicity
- Immunotoxicity
- Acute toxicity
- Repeat dose (chronic) toxicity

Abuse Liability

- Nonuser initiation (including youth)
- Former user relapse
- User switching to higher risk product
- Dual use
- Nonuser exposure (accidental/second hand)
- Device malfunction (e.g., explosion, leaking)

Context for Risk Assessment in PMTA

- Under § [1114.7\(k\)\(1\)\(i\)\(B\)](#), a PMTA must contain... the toxicological profile of the new tobacco product related to the route of administration, including, but not limited to, the genotoxicity, carcinogenicity, respiratory toxicity, cardiac toxicity, reproductive and developmental toxicity, and chronic (repeat dose) toxicity of the new tobacco product relative to other tobacco products.
- For ingredients, leachables, and harmful and potentially harmful constituents (HPHCs), applicants have included a range of data and justifications for:
 - Hazard identification
 - Hazard assessment
 - Exposure assessments
 - Risk assessments

Hazard Identification for ENDS Risk Assessment

- Toxicological hazards can originate from **direct addition** of ingredients to the product or through the **degradation, combustion, and pyrolysis** of these chemicals.
- Many harmful and potential harmful constituents (HPHCs) are both cancer and non-cancer hazards (e.g., acetaldehyde and formaldehyde)
- Ingredients and leachables from ENDS devices may also be cancer and non-cancer hazards
- During user exposure, all these toxicological hazards are present in a mixture
 - For ENDS, ingredients and leachables, along with HPHCs, contribute to overall risk
 - Minimizing added ingredients and unintended leachables that are toxicological hazards may lower risks

Examples of Toxicants Found in ENDS

This is a non-exhaustive sample of toxicants found in ENDS

Some toxicants such as aldehydes are present to varying degrees in all ENDS

Other toxicants, such as E-liquid ingredients, vary from product to product.

Category	Constituent	Cancer	Noncancer	Evidence Base (Cancer; Noncancer)
Metal	Nickel	Lung and Nasal	Respiratory, DART, Multiple Health Outcomes	IARC Group 1; human and in vivo evidence
	Cadmium	Lung, liver, prostate	Respiratory; Multiple Health Outcomes	IARC Group 1; human and in vivo evidence
	Lead	Kidney	CNS; Multiple Health Outcomes	EPA B2; Human evidence
Plastic	Bisphenol A	Genotoxicity	Endocrine; Multiple Health Outcomes	Positive in vivo Chrom Ab; in vivo evidence of carcinogenicity
	Pthalates	Colorectal, breast, prostate, thyroid	Endocrine; Multiple Health Outcomes	IARC 2B; In vivo evidence
Aldehyde	Formaldehyde	Myeloid Leukemia, nasal	Respiratory; Multiple Health Outcomes	IARC Group 1; Human, in vivo, and in vitro evidence
	Acetaldehyde	Aerodigestive (oral and nasal)	Respiratory; Multiple Health Outcomes	IARC 2B; Human or in vivo evidence
E-liquid Ingredient	Maltol	Genotoxicity	Hepatic and Renal; Multiple Health Outcomes	Positive in vivo MN; In vivo evidence
	Pulegone	Liver and Bladder	Hepatic; Multiple Health Outcomes	IARC 2B; In vivo evidence

Uncertainty in Risk Assessment

- One of the first steps in risk assessment, Hazard Identification, is critical to the development of tobacco product toxicity profiles, because tobacco products have so many more toxicants than other consumer products.
- Toxic constituents present in tobacco products can have extremely well documented toxicity profiles, or they may have indications of toxicity supported by varying levels of empirical data. For example:
 - A constituent may have sufficient empirical data to be on the HPHC list
 - A constituent may have been recently designated as a carcinogen by IARC
 - A constituent may be positive in the Ames assay, an assay that is 80 – 90% predictive of carcinogenicity
 - A constituent may have no in vivo or in vitro toxicity information available, but a computational model of the Ames assay, which is also ~80% predictive of carcinogenicity, may predict a positive Ames result

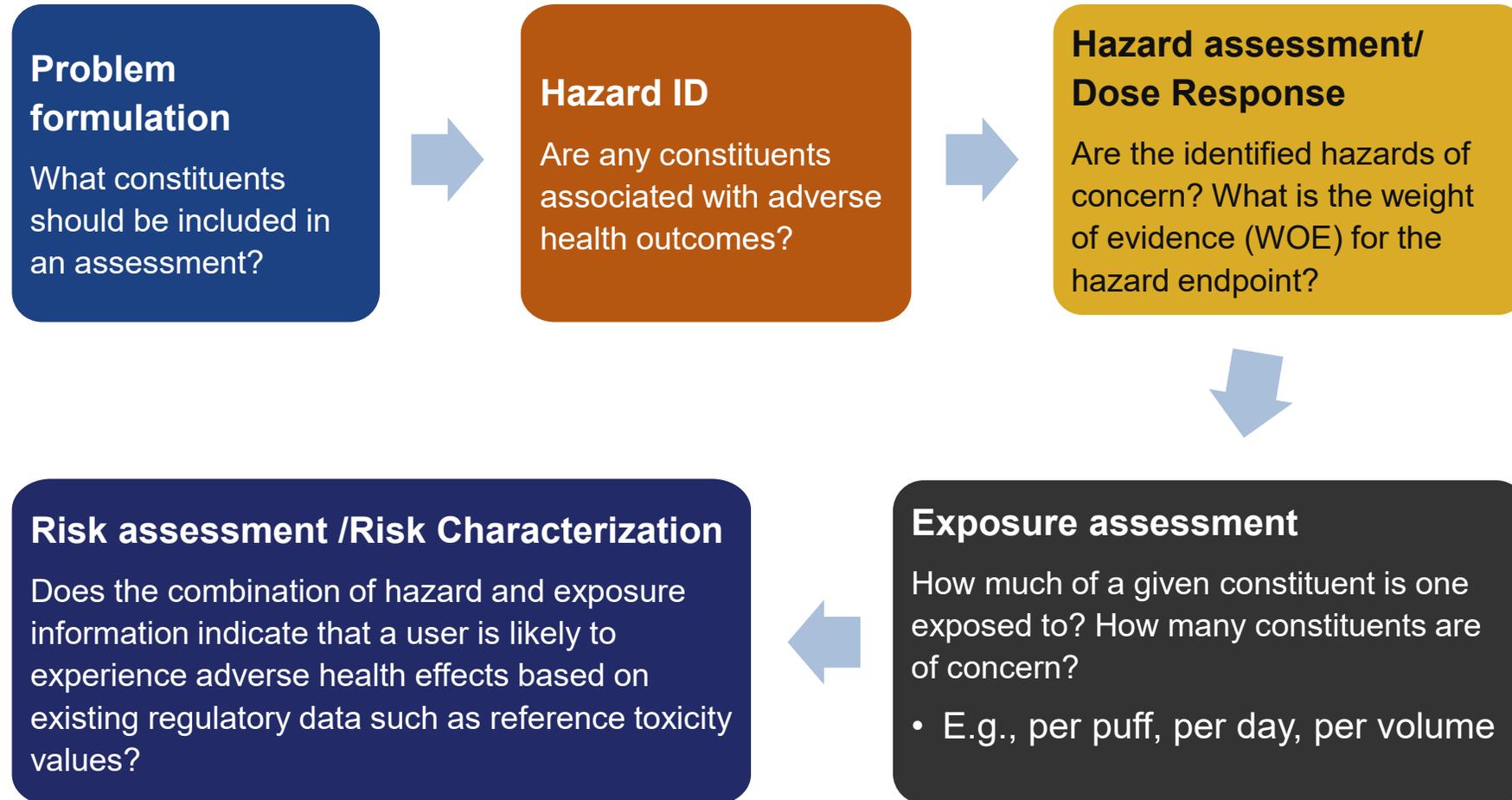
Uncertainty in Risk Assessment

- One might be tempted to include only toxicants with the most documentation – such as only HPHCs or only IARC designated carcinogens in a tobacco product risk assessment.
 - But rather than being more rigorous, such an approach would miss much of the toxicity of a tobacco product, because only a very few tobacco constituents have the highest level of documentation (such as an epidemiology study or a well-controlled rodent carcinogenicity study)
 - For example, out of 10 Ames positive chemicals, an average of 8-9 constituents are predicted to be genotoxic carcinogens that cause tumors in a rodent assay. Therefore:
 - Not including Ames positive constituents in a risk assessment would throw out a lot of actual tobacco product risk
- To account for levels of certainty in hazard identification, FDA has used a tiering system in its scientific review of PMTAs

Cancer Hazard Tiering

- While the toxicological profile of a tobacco product entails both cancer and noncancer hazards, today we can provide more detail on managing estimated lifetime cancer risk (ELCR)
- We are now going to transition a short presentation on how cancer hazard tiering can help manufacturers manage the cancer risk posed by their tobacco products.
- Dr. Mary Irwin will discuss an approach to such tiering, which are described in more detail in FDA science policy memos:
 - June 03, 2024: Genotoxicity Hazard Identification and Carcinogenicity Tiering of Constituents in ENDS Premarket Tobacco Product Applications
 - June 03, 2024: Calculating Excess Lifetime Cancer Risk in ENDS Premarket Tobacco Product Applications
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Risk Assessment Process



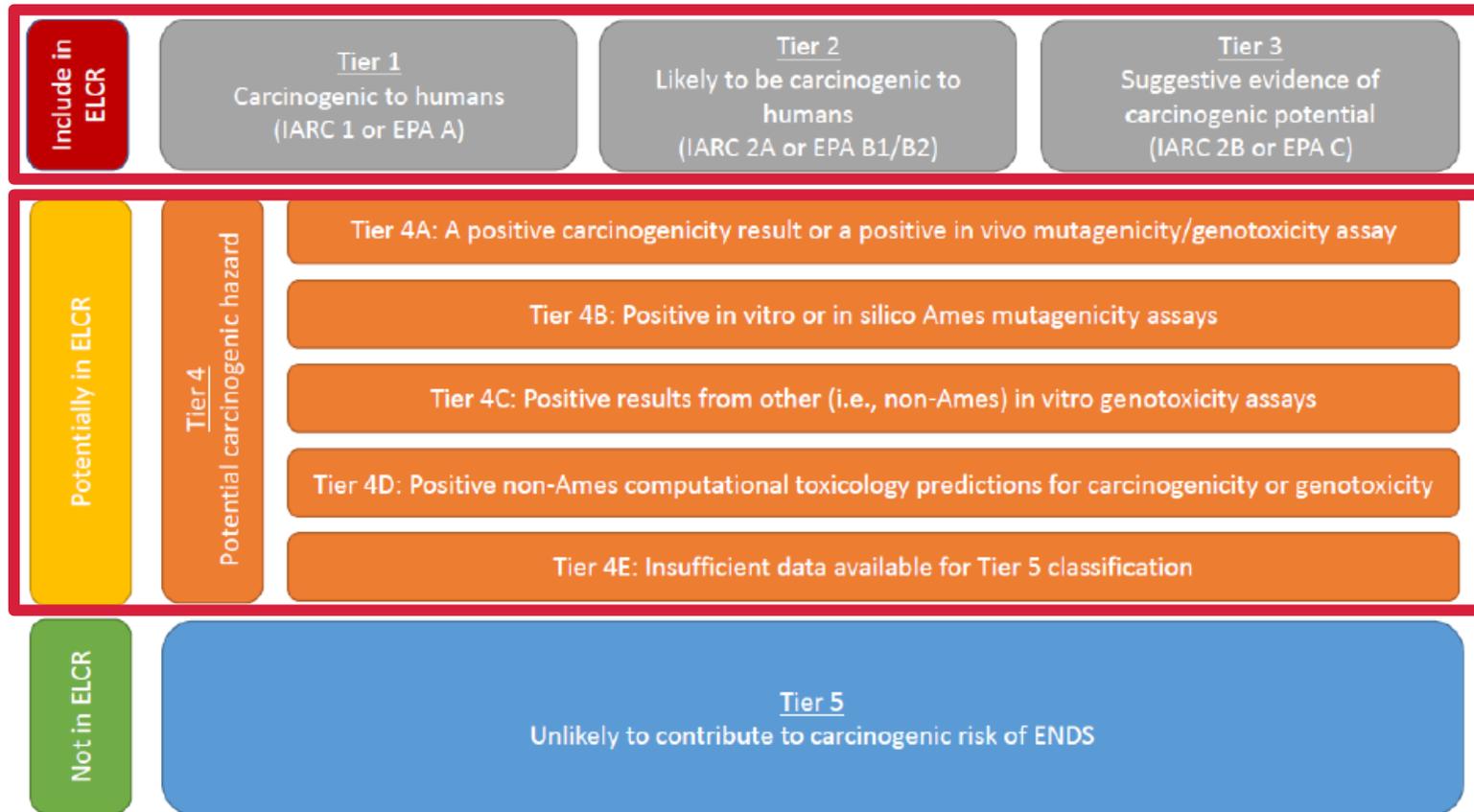
Information needed for Risk analyses

- How much of the new product does a user use per day? (90th percentile of use, if not available, 40 mg nicotine equivalent will be used)
- HPHCs
 - Measured levels of HPHCs from a new product
 - All known hazard information regarding HPHCs that are above LOQ/LOD
- Ingredients
 - Amounts of ingredients added to the e-liquid formulation of a new product
 - All known hazard information regarding ingredients
- Leachates
 - Measured leachables from devices and container closure systems (e.g., coil, wick, e-liquid cartridge)
 - All known hazard information regarding measured leachates

Genotoxicity Hazard Identification and Carcinogenicity Tiering

Based on weight of evidence (WoE) for carcinogenicity, constituents are placed into one of five tiers:

Decision trees for inclusion of a constituent in ELCR assessment following tiering classification



Tiers 1-3 are limited to constituents previously **classified by EPA and IARC**. Toxicology reviewers do not classify constituents that have not been previously evaluated by EPA or IARC into Tier 1-3.

Constituents not evaluated by EPA or IARC but with data that support a potential carcinogenicity or genotoxicity concern, or constituents classified as EPA Group D or IARC Group 3, are classified as Tier 4. A broad range of evidence, including human, animal, in vitro, and computational data, is appropriate for a Tier 4 classification. Tier 4 constituents are further categorized into subgroups A-E based on the strength of supporting data to reflect varying levels of concern for carcinogenicity.

Tier 5 Constituents are Not Included In ELCR

Tier 5 WOE considerations: Unlikely to contribute to carcinogenic risk of ENDS

Minimum requirement:

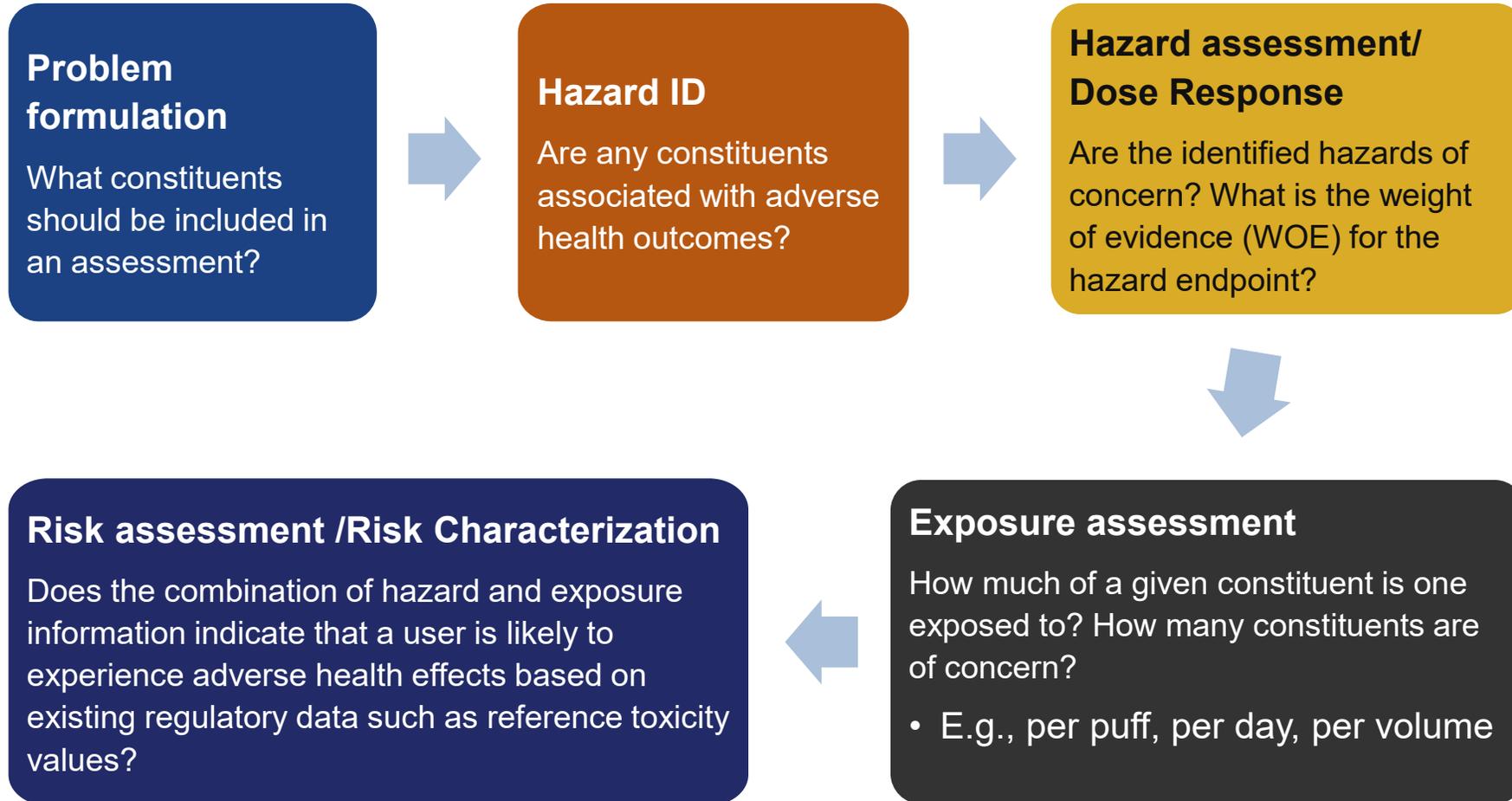
- Tier 5 classification may be appropriate based upon genetic toxicology evidence alone:
 - **One negative finding for mutagenicity** from an in vitro, in vivo, or computational test, and
 - **One negative finding for chromosomal damage** from an in vitro or in vivo test, and
 - No positive or equivocal predicted outcomes from **computational toxicology** evaluations

Example Constituent	Justification
D'Limonene	Negative Ames Negative in vitro HPRT Negative chromosomal aberration Negative NCTP Predictions for Carcinogenicity
Ethyl Vanillin	Negative Ames Negative Chrom Aberration Negative NCTP prediction for Carcinogenicity Negative in vivo MN (not used for WoE due to lack of target tissue exposure data)
Isobutyraldehyde	Positive MLA Negative Ames Positive Chromosomal Aberration Negative Inhalation Carcinogenicity in Rats and Mice

Taking Route of Administration Into Account

- FDA has determined the safety of flavor chemicals in the context of food based on oral route of exposure (e.g., GRAS designation by FDA)
- Often, these designations use in vivo genotoxicity studies or carcinogenicity studies based on oral route of administration in a weight of evidence analysis to dismiss in vitro genotox findings
- However, **ENDS are inhaled products**:
 - Inhaled constituents are not subject to first-pass metabolism in the liver prior to systemic circulation
 - Inhaled constituents may be bioactivated locally in the lung or conducting airways (e.g., NNK)
 - Direct access to systemic circulation may increase target tissue exposure
- Therefore, it is important to verify in a weight of evidence analysis that:
 - in vivo carcinogenicity studies used in a weight of evidence analysis have a relevant route of exposure for the reported endpoint.
 - in vivo genotoxicity studies provide data confirming target tissue exposure. For example, first pass metabolism may prevent exposure of sampled tissue to test article.

Cancer Risk Assessment



What is an ELCR Assessment

- ELCRs are **estimates** of cancer risk
 - Such estimates are especially important when epidemiological data to quantify actual cancer risk is lacking
 - Thus, ELCRs are especially important for ENDS because insufficient time has passed for the conduct for long-term epidemiology studies
 - This analysis depends on the strength and number of assumptions and an overall WOE approach
- Potential excess lifetime cancer risk (ELCR) can be determined for an individual product
- $\text{ELCR} = \text{Daily exposure of a constituent} / \text{Potency value (adjusted inhalation unit risk value (IUR) or threshold of toxicological concern (TTC))}$
- Cumulative ELCR (ELCR_c) = Σ ELCR from all cancer hazard constituents
- ELCR_c can then be compared among tobacco products

How to Calculate ELCR

- All cancer hazards (Tier 1-4C; including HPHCs, Ingredients, and leachables) are included in the ELCR
 - If aerosol amounts are not measured, the assumption is 100% exposure based on the amount present
 - If there is no adjusted IUR, the TTC of 1.5 ug/day is used for a reference value
- The cumulative ELCR (ELCR_c) is the sum of all constituent ELCRs >1 (i.e., all cancer hazards Tier 1-4C), so additivity is assumed.
- Tiers 4D and 4E only are considered if their ELCR values would change the risk descriptor relative to the marketplace/1R6F cigarette

Comparisons are made to aid decision making

- Comparison to the same product category and subcategory (i.e., the ENDS Median of 264 per 100,000)
- Other categories as appropriate (i.e., a reference cigarette, 1R6F, value of 19,954 per 100,000)
- Qualitative Risk Management Descriptors are used to convey relative risk to the TPL

Table 1. Qualitative Risk Management Descriptors

% of 1R6F ELCR _c	Descriptor	ELCR _c Range	Calculated Cancer Risk
< 1.0%	Lower Concern	≤200	≤ 1:501
1-10%	Moderate Concern	201-1,995	1:500-1:50
10-25%	Increased Concern	1,996-4,988	1:49-1:20
25-50%	Elevated Concern	4,989-9,977	1:19-1:10
> 50%	Serious Concern	≥9,978	≥1:09

How Can One Reduce Cumulative ELCR?

How to Reduce ELCR – Product Design

- Use higher quality materials that do not have hazardous leachates
- Formulate flavoring with tier 5 constituents
- Example:
 - Product A has ELCR from HPHCs of 8, uses BPA-free pharmaceutical grade plastics for design and therefore has a single leachate that is tier 4C at 0.1 ug/day, and its flavoring ingredients are all tier 5: The cumulative ELCR of this product is 8 per 100,000
 - Product B has the same ELCR from HPHCs of 8 but uses a lower quality plastic so leachates like BPA (Tier 4A) and Di (2-ethylhexyl) phthalate (DEHP) (tier 3) are present contributing a total of 900 ELCR, and flavoring ingredients add an additional 200 ELCR (Tiers 1-4C). The cumulative ELCR of this product is 1,108 per 100,000.
- Products A and B have the same HPHC profile, however due to choices made in manufacturing and formulation, the ELCR of Product B is much higher.

Conclusions

- Toxicity of ENDS products varies from product to product
- The toxicity is largely from manufacturing and formulation design elements that an applicant can control
- Excess lifetime cancer risk calculations can give an estimate of cancer risk
 - More accurate estimates come with better hazard identification and exposure information
 - Hazard ID depends on route of exposure
- While this presentation focused on ELCRs, the consideration of non-cancer risks is also influential to toxicology conclusions
- The way one designs their product influences the toxicological risks of the product itself. Ways to minimize risk include:
 - Using formulation ingredients that do not have cancer/non-cancer toxicities (e.g., Tier 5 constituents)
 - Using better quality materials that have innocuous leachates

Additional Slides

Adjusted IURs

Constituent	IUR (µg/m ³) ⁻¹	Source	Adjusted IUR (µg/day) associated with 1 in 100,000 ELCR
1,3-Butadiene	3.00E-05	(EPA, 2002)	8.974
2-Aminonaphthalene	5.14E-04	(CalEPA, 1992c)*	0.524
2-Nitropropane	5.80E+02	(EPA, 2019)	0.00000046
4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	1.40E-02	(CalEPA, 2001)*	0.019
4-Aminobiphenyl	6.00E-03	(CalEPA, 1992a)	0.0449
5-Methylchrysene	1.10E-03	(CalEPA, 2009a)	0.245
Acetaldehyde	2.20E-06	(EPA, 1988)	122.378
Acetamide	2.00E-05	(CalEPA, 2009b)	13.462
Acrylamide	1.00E-04	(EPA, 2010)	2.692
Acrylonitrile	6.80E-05	(EPA, 1987a)	3.959
Arsenic	4.30E-03	(EPA, 1995)	0.0626
Benz[a]anthracene	6.00E-05	(TCEQ, 2017)	4.487
Benzene	7.80E-06	(EPA, 2000a)	34.517
Benzo[a]pyrene	1.00E-03	(EPA, 2017)	0.269
Benzo[b]fluoranthene	6.00E-05	(TCEQ, 2017)	4.487
Benzo[k]fluoranthene	1.10E-04	(CalEPA, 2011a)	2.448
Beryllium	2.40E-03	(EPA, 1998)	0.112
Cadmium	1.80E-03	(EPA, 1987b)	0.150
Chlorinated dioxins/furans	1.30E+00	(EPA, 1987c)^	0.00021
Chloroform	2.30E-05	(EPA, 2001)	11.706
Chromium	1.80E-02	(EPA, 2024b)	0.015
Chrysene	1.10E-05	(CalEPA, 2011b)	24.476
Cobalt	9.00E+02	(EPA, 2008)	0.000000299
Crotonaldehyde	3.27E-05	(TCEQ, 2015)	8.233
Di(2-ethylhexyl)phthalate	2.40E-06	(CalEPA, 2011c)	112.179
Dibenzo[a,h]anthracene	1.20E-03	(CalEPA, 1992b)	0.224
Dibenzo[a,e]pyrene	1.10E-03	(CalEPA, 2025b)	0.245
Dibenzo[a,h]pyrene	1.10E-02	(CalEPA, 2025a)	0.0245
Dibenzo[a,i]pyrene	1.10E-02	(CalEPA, 2025b)	0.0245
Dibenzo[a,l]pyrene	1.10E-02	(CalEPA, 2025c)	0.0245
Dichloromethane	1.00E-08	(EPA, 2011)	26,923.077

Constituent	IUR (µg/m ³) ⁻¹	Source	Adjusted IUR (µg/day) associated with 1 in 100,000 ELCR
Ethylbenzene	2.50E-06	(CalEPA, 2010)	107.692
Ethylene oxide	5.00E-03	(EPA, 2016)	0.0538
Formaldehyde	1.10E-05	(EPA, 2024a)	24.476
Glu-P-1 (2-Amino-6-methylpyrido[1,2-a:3',2'-g]imidazole)	1.40E-03	(CalEPA, 1992c)	0.192
Glu-P-2 (2-Aminodipyrdo[1,2-a:3',2'-g]imidazole)	4.00E-04	(CalEPA, 1992c)	0.673
Hydrazine	4.90E-03	(EPA, 2009)	0.0549
Indeno[1,2,3-cd]pyrene	1.10E-04	(CalEPA, 2009d)	2.448
IQ (2-Amino-3-methylimidazo[4,5-f]quinoline)	4.00E-04	(CalEPA, 1992c)	0.673
Isoprene	5.40E-06	(CalEPA, 2025d)	49.858
Lead	1.20E-05	(CalEPA, 2009c)	22.436
Naphthalene	3.40E-05	(ATSDR, 2022)	7.919
Nickel	2.40E-04	(EPA, 1987e)*	1.122
Nitromethane	8.80E-01	(EPA, 1997)	0.000306
N-Nitrosodiethanolamine (NDELA)	8.40E-04	(CalEPA, 1992c)	0.321
N-Nitrosodiethylamine	4.30E-02	(EPA, 1984)	0.00626
N-Nitrosodimethylamine (NDMA)	1.40E-02	(EPA, 1987d)	0.0192
N-Nitrosomethylethylamine	6.30E-03	(CalEPA, 2011d)	0.0427
N-Nitrosomorpholine (NMOR)	1.90E-03	(CalEPA, 2011d)	0.142
N-Nitrososornicotine (NNN)	4.00E-04	(CalEPA, 1992c)	0.673
N-Nitrosopiperidine (NPIP)	2.70E-03	(CalEPA, 2011d)	0.100
o-Anisidine	4.00E-05	(CalEPA, 1992c)	6.731
o-Toluidine	5.10E-05	(CalEPA, 1992c)	5.279
Propylene oxide	3.70E-06	(EPA, 1990)	72.765
Styrene	7.43E-06	(CalEPA, 2016)*	36.243
Trp-P-1 (3-Amino-1,4-dimethyl-5H-pyrido[4,3-b]indole)	7.40E-03	(CalEPA, 1992c)	0.0364
Trp-P-2 (1-Methyl-3-amino-5H-pyrido[4,3-b]indole)	9.10E-04	(CalEPA, 1992c)	0.296
Vinyl chloride	8.80E-06	(EPA, 2000b)	30.594

* IUR is calculated from a cancer potency value (e.g. mg/kg-day)⁻¹ assuming 70 kg body weight and daily inhalation rate of 20 m³/day; ^EPA IUR is based on Hexachlorodibenzo-p-dioxin (HxCDD), mixture of 1,2,3,6,7,8-HxCDD and 1,2,3,7,8,9-HxCDD; * IUR is based on chromium (IV); *IUR is based on nickel refinery dust.

Questions or Comments?

Contact CTP	AskCTP@fda.hhs.gov 1-877-287-1373
Docket (Closes March 12, 2026)	www.Regulations.gov Docket no. FDA-2025-N-7022
HHS Press Room	202-690-6343