# FDA REGULATION UPDATE

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*Disclaimer: This is not a formal dissemination of information by FDA and does not represent Agency position or policy.*

- Strategic Plan in Brief
- PMTA APPH Update
- Genotoxicity
- Adult Benefit

# CTP'S 5-YEAR STRATEGIC PLAN

**Goal 1**: Develop, Advance, and Communicate Comprehensive and Impactful Tobacco Regulations and Guidance

**Goal 2:** Ensure Timely, Clear and Consistent Product Application Review

**Goal 3:** Strengthen Compliance of Regulated Industry Utilizing All Available Tools, Including Robust Enforcement Actions

**Goal 4:** Enhance Knowledge and Understanding of the Risks Associated With Tobacco Product Use

**Goal 5:** Advance Operational Excellence

# OS PUBLIC MEETING & TPSAC MEETING

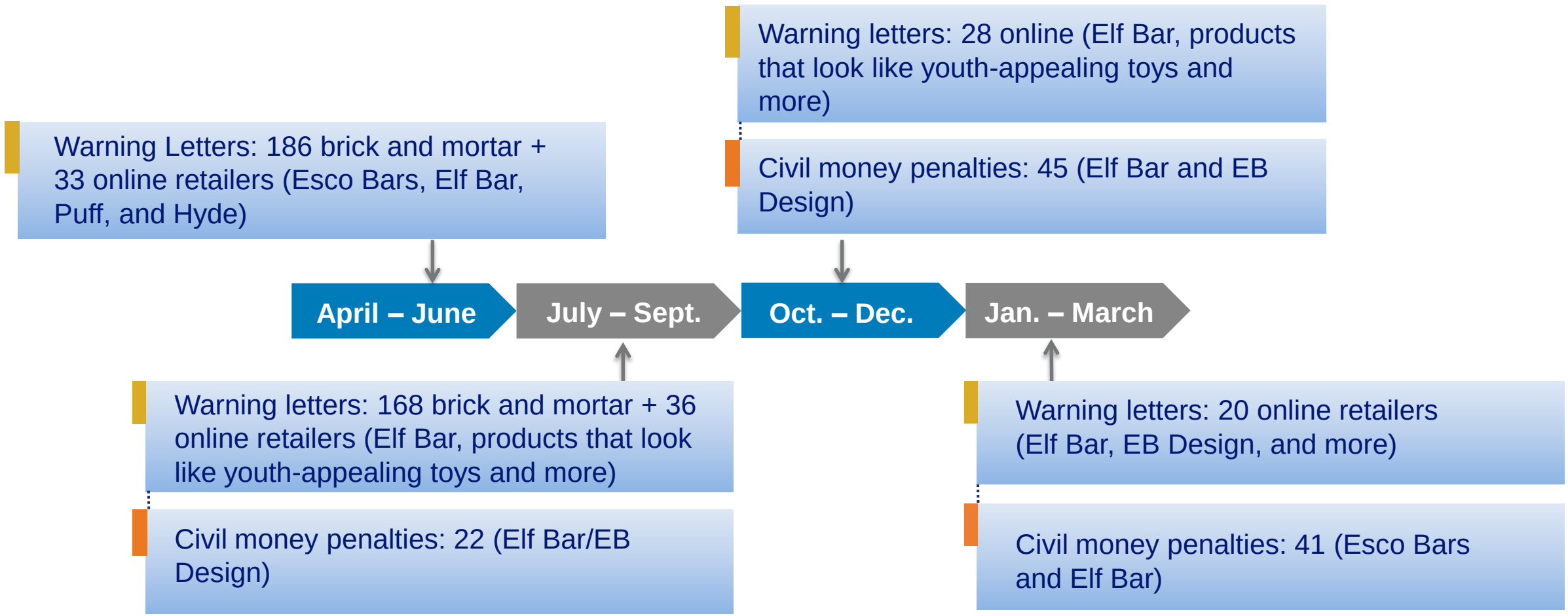

- **October 2023:** Public Meeting on the agency's expectations for SE Reports and PMTAs, highlighting the now required content for SE and PMTA per the final rules

- **April 2023:** Tobacco Products Scientific Advisory Committee (TPSAC) met to discuss the "Requirements for Tobacco Product Manufacturing Practice" proposed rule

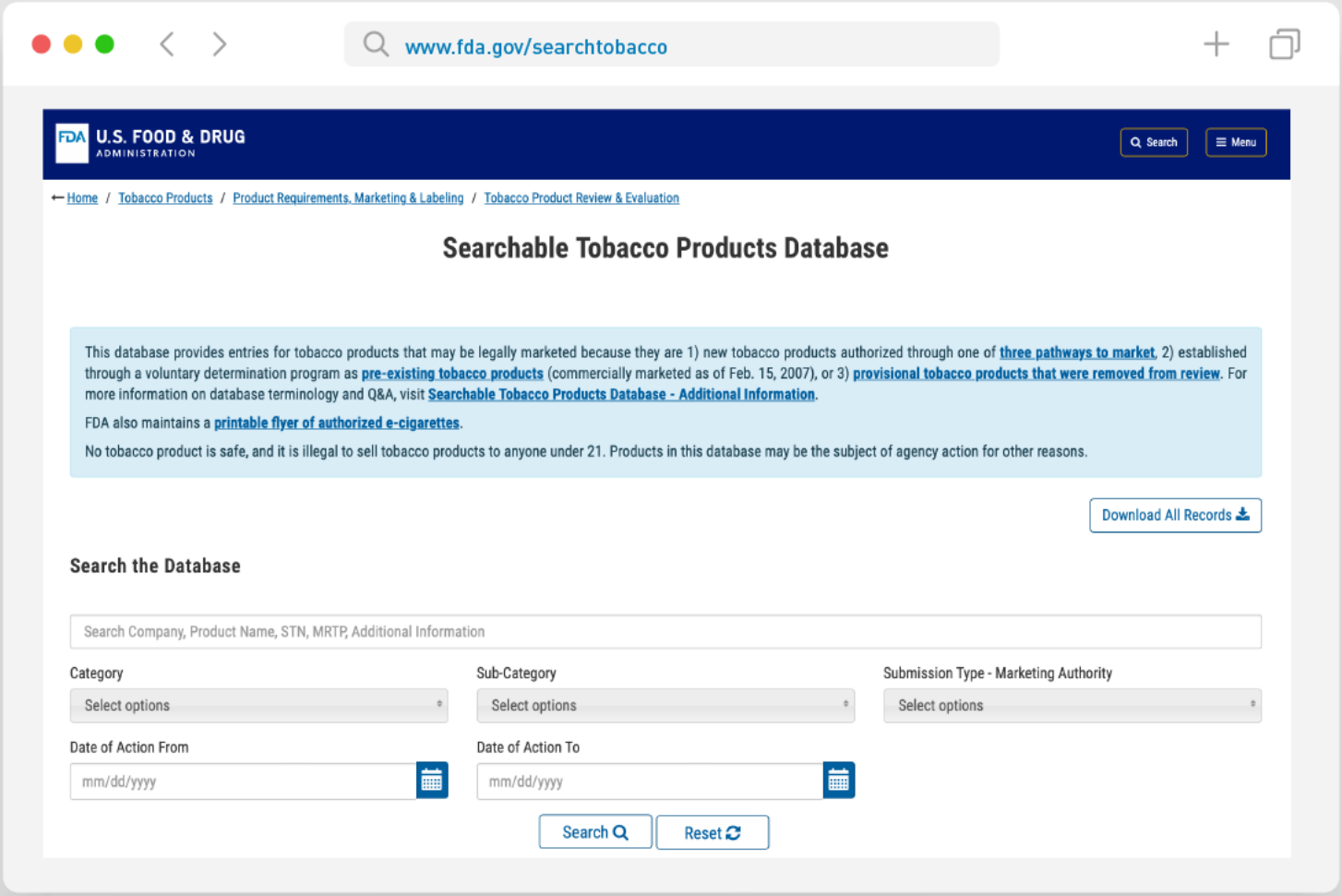
# OS POLICY MEMOS

- Developed to assist FDA reviewers with the evaluation of new tobacco product applications
- Eleven released to date, covering topics pertaining to Science and Processes within the tobacco product application program and review processes
- Posted online in response to public interest
- Provides a snapshot of CTP's internal thinking on certain aspects of tobacco regulatory science covering topics

# RECENT ACTIONS AGAINST RETAILERS SELLING UNAUTHORIZED E-CIGARETTES POPULAR WITH YOUTH



# SEARCHABLE TOBACCO PRODUCTS DATABASE




www.fda.gov/searchtobacco

# PMTA AND APPH UPDATE

# OVERVIEW

- FDA's job is to assess the applicant's scientific evidence to determine if marketing of the tobacco product is appropriate for the protection of the public health
- During the fall public meeting, attendees expressed an interest in understanding how CTP determines whether a product meets the APPH standard
- We delivered scientific presentations around hazard identification; quantifying cancer risks; considerations for conducting and analyzing randomized controlled trials and longitudinal cohort studies to quantify adult benefits among other topics
- Today I'll revisit highlights of two key topics that help inform decisions around APPH

# OVERVIEW (2)

- APPH determinations cannot be reduced to a simple checklist or formula
- For ENDS, key considerations are:
  - Magnitude and strength of benefit for adult users;
  - Health risks (e.g., cancer, non-cancer) of new product
  - Risks of initiation by non-users/never users (e.g., youth), influenced by factors such as the appeal and abuse liability of the product
  - Mitigation strategies to prevent/discourage youth use
- Today, I'll briefly review considerations for longitudinal cohort studies that can be used to quantify adult benefit and toxicology methods that inform health risk assessments

# TOXICOLOGY CONSIDERATIONS IN PMTAS

# TOXICOLOGY TESTING OF ENDS PRODUCT

- PMTA ENDS reviews has focused on comparison of the level of HPHCs
- Does not capture constituents in ENDS not present in cigarettes
- ENDS products exposure to genotoxicants that induce adverse effects on genetic components (e.g., DNA) through a variety of mechanisms:
  - Thermal degradation or reaction products of e-liquid constituents that transfer to the aerosol
  - E-liquid ingredients that transfer directly to the aerosol
  - Leachables that migrate from ENDS container closure systems and components into the e-liquid and transfer to the aerosol
- When ENDS e-liquids are aerosolized, they are known to produce genotoxic carbonyl compounds formaldehyde and acetaldehyde

# CHALLENGES IN TESTING E-LIQUID AND AEROSOL MIXTURES

- The goal of hazard ID testing is to identify whether individual constituents in ENDS products are genotoxic (yes/no).
  - These assays do not provide relative assessments of genotoxicity
- Hazard identification assays for genotoxicity are not well-suited to complex mixtures, because of the presence of multiple, known genotoxicants
- OS has identified several concerns related to genotoxicity studies submitted with applications, which limit their utility in genotoxicity assessments
- Because these tests cannot provide relative assessments of ENDS e-liquids and aerosols and they contain multiple known genotoxicants, OS discussed testing individual constituents rather than whole mixtures in the fall public meeting

# TESTING INDIVIDUAL CONSTITUENTS

- Because of the challenges, FDA will seek to understand the underlying genotoxicity of the constituents, ingredients, and chemicals contained in the mixture
- While there is a wealth of information on the toxicities of some ENDS constituents, others are data-limited or have conflicting hazard outcomes (i.e., both positive and negative study results) making it difficult to confidently assess genotoxicity
- While we recognize that some ENDS' constituents have the potential to convey non-cancer risks, the current focus is on cancer risks
- Constituents are evaluated for genotoxicity hazards and cancer risk using a combination of hazard identification assays, scientific literature, and toxicological database searches

# TIERING OF RISKS

- Tier 1: Carcinogenic to humans: linked to IARC Group 1
- Tier 2: Likely to be carcinogenic to humans: linked to IARC Group 2A
- Tier 3: Suggestive evidence of carcinogenic potential: Linked to IARC Group 2B
- Tier 4: Potential carcinogenic hazard
  - 4a: have evidence of carcinogenicity or genotoxicity in humans or in vivo model systems
  - 4b: have a positive finding for mutagenicity from at least one in vitro Ames assay
  - 4c: have a positive finding from at least one other (i.e., non-Ames) in vitro genotoxicity assay.
  - 4d: positive non-Ames computational toxicology predictions for carcinogenicity or genotoxicity
  - 4e: have insufficient data available for a Tier 5 classification that do not fit into other tiers
- Tier 5: Unlikely to contribute to carcinogenic risk of ENDS

# GENOTOXICITY HAZARD ID: TOOLS FOR WEIGHT OF EVIDENCE (WOE) EVALUATION OF DATA-POOR CHEMICALS

- Data-poor chemicals
  - Chemicals with no information
  - Conflicting genotoxicity results (e.g., clear positive and negative)
  - Studies with positive results that have methodological issues that prevent a confident conclusion (e.g., issues with study design or statistical power) may be considered as data-poor chemicals
- New Approach Methods (NAMS), such as ‘Computational Toxicology’ tools may be used for identifying genotoxicity in data-poor chemicals:
  - Predicted by (Q)SAR to be Ames positive using computational approaches
  - Predicted positive using read across from a known carcinogen
  - High throughput clastogenicity screening (Hung, 2020)

# WHERE WOE INDICATES GENOTOXIC RISK

- Calculate Excess Lifetime Cancer Risk (ELCR) using Inhalation Unit Risk (IUR)
- Where IUR does not exist, seek alternative sources of risk
  - Additional information may be requested for Tier 4 ingredients
- Where alternative information is not provided
  - Assume 100% transfer from e-liquid to aerosol
    - Data supporting alternative transfer rates should be developed using a specific, validated quantitative method
  - Use a Threshold of Toxicological Concern (TTC) value of 1 in 100,000 (1.5 ug/day) for exposure

# EXCESS LIFETIME CANCER RISK

- One way to evaluate the cancer risk of tobacco products is to calculate an excess lifetime cancer risk (ELCR), which provides an extrapolated estimate for how many additional cases of cancer would be expected in a population exposed to a given toxicant concentration and intake level for an entire lifetime based on the toxicant's carcinogenic potency.
- ELCRs can be calculated for each constituent that is associated with cancer health effects, and then summed to determine a cumulative ELCR. This is useful for ENDS where no long-term cancer studies are available.
- ELCRs provide a consistent estimate of cancer risk in new products (e.g., ENDS) and allow a comparative analysis to other tobacco products (e.g., combusted cigarettes).
- To consistently assess the potential cancer risk of new ENDS products, OS will compare the ELCR for a new ENDS product and to the ELCR for a reference combusted cigarette (1R6F).

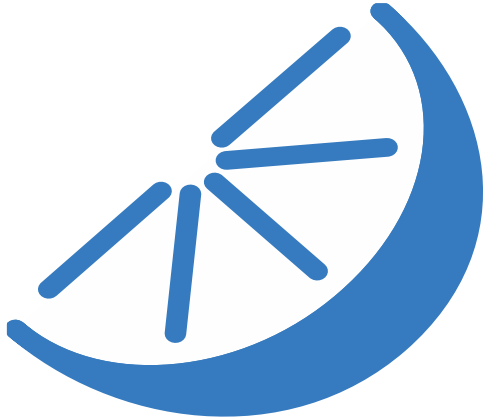
# BRINGING IT TOGETHER

- The ELCR analysis uses methods consistent with the general risk assessment framework used by EPA for Air Toxics Assessment (US EPA, 2018).
- When available, it relies on EPA and IARC to classify the cancer risk of ENDS constituents.
- When there are constituents of concern that have not been evaluated by EPA/IARC, OS will conduct a weight-of-evidence approach to assess potential human cancer risk.
- These concerns may be communicated to applicants so they can address these potential concerns.
- The final determination of the cancer risks of an ENDS product compared to CC and with previously authorized ENDS will be considered as one factor in our APPH determination.

# LONGITUDINAL COHORT STUDIES

# REVIEW OF FLAVORED ENDS PMTAS

- Preventing youth use is a key consideration.
- The risks to youth posed by flavored ENDS are substantial and well-established.
- FDA has concluded that non-tobacco flavored ENDS, including menthol-flavored ENDS, present **significant risk** to youth with respect to appeal, uptake, and use.
- For PMTA review, the term “flavored ENDS” refers to an ENDS product with any characterizing flavor other than tobacco, including menthol flavor.
- We have a streamlined approach for flavored ENDS PMTA reviews such that we do a targeted review first to see if there are data (e.g., RCT/LCS) that speak to adult benefit. In absence of this evidence, the application receives a denial order.



RCT = Random Control Trials
LCS = Longitudinal Cohort Study

# FLAVORED ENDS LITERATURE: ADULT BENEFIT

- No ENDS products have been approved by FDA-CDER as a smoking cessation therapy
- A growing body of clinical and observational evidence suggests that ENDS can contribute to smokers transitioning away from cigarettes.
  - 2022 Cochrane Review concludes: There is high-certainty evidence that electronic cigarettes with nicotine increase quit rates compared to nicotine replacement therapy (NRT)
- However, based on systematic reviews of RCTs and observational studies, the role of flavored ENDS, in particular, for adult smoking cessation remains unclear due to limited data and mixed findings.

Source: Hartmann-Boyce, Lindson et al. Cochrane Database Syst. Rev. 2022

# CONSIDERATIONS DURING PMTA REVIEW OF FLAVORED ENDS

- In reviewing PMTAs for flavored ENDS products, FDA considers whether there is sufficient evidence of an added benefit from the flavored ENDS relative to that of tobacco-flavored ENDS in facilitating adults who use combustible cigarettes in completely switching from or significantly reducing their smoking.
- This evidence of added benefit is needed to outweigh the risks of the flavored ENDS product—risks to youth initiation and other health risks
- By contrast, tobacco-flavored ENDS raise a different set of considerations because they do not pose the same degree of risk of youth uptake

# COHORT STUDY DESIGN CONSIDERATIONS

- **Cohort studies** of ENDS have cost/benefit tradeoffs compared to trials:
  - Less expensive to conduct, offering relatively large sample sizes
  - Can provide a naturalistic or “Real World” setting within actual user or purchaser populations
  - Risk of loss to follow-up and residual or unobserved confounders
- Well-established frameworks such as STROBE provide guidelines for reporting of design, analysis, results, and conclusions

Sources: von Elm et al, 2007; Tooth et al, 2005; and National Heart, Lung, and Blood Institute’s study quality assessment tools

# CONSIDERATIONS FOR LONGITUDINAL COHORT STUDIES

- Tooth et al (2005) study on Quality of Reporting of Observational Longitudinal Research provides helpful examples of how to report longitudinal cohort study descriptions. Specifically:
  - Is the sampling frame defined?
  - Are the eligibility stated?
  - Are the numbers of people who did/did not consent to participate stated?
  - Was the number of participants at the beginning of the study stated?
  - Were methods of data collection stated?
  - Were any confounders mentioned? (I would add, described)
  - Was the number of participants at each stage/wave specified?
  - Were the analytic methods described?

# CONSIDERATIONS FOR LONGITUDINAL COHORT STUDIES (2)

- While carefully describing studies is more straightforward to implement, the consequences of implementing analytic approaches/decisions are harder to easily summarize as they can be very study/context dependent.
- In any case, examples from Tooth, et. al. do point to potentially important analytic considerations:
  - Were absolute and relative effect sizes reported?
  - Was loss to follow-up taken into account in the analysis? (if so, how?)
  - Was the impact of biases assessed qualitatively/quantitatively?
- Although longitudinal cohort studies may reflect real world contexts, they may also be affected by loss to follow-up and/or bias that can influence the interpretation of study findings.

# COHORT STUDY CONSIDERATIONS: POPULATION AND RECRUITMENT

- Any added adult benefits of flavored ENDS vs. tobacco ENDS are primarily assessed in **current established users of combusted cigarettes**
- Participants can be **recruited as new or current ENDS users**, or **provided ENDS products** after study enrollment
  - If products are currently marketed internationally, truly observational studies can be conducted
  - If products are not marketed, they can be provided products (a.k.a. an “actual use study”)
- **Recruitment** for observational studies can utilize **diverse channels**
  - e.g., in-package or online sales, online research panels, e-mail, messaging apps, social media
  - Recruitment channels or pooled analyses should be appropriate and justified
- FDA reviews for rationale and justification for **sample size**

# COHORT STUDY CONSIDERATIONS: EXPOSURE

- Typically, in observational studies, participants do not receive additional instructions on product use
- **Flavor use can be dynamic** over the duration of a study. Assessments of flavors used at each point of follow-up might include:
  - Exclusive use of any one flavor
  - Primary use of any one flavor
  - Roughly equal use of two or more flavors
  - Experimentation with any flavors
  - All flavors used
- Analyses should adjust appropriately (e.g., for use of other tobacco or cessation products)
- Assessments of flavors and products used should be **quantitative and justified**

# COHORT STUDY CONSIDERATIONS: OUTCOMES

- **Complete switching** as a primary outcome
  - Typically, complete cigarette abstinence (past 7-day or past 30-day)
  - 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)
- **Significant CPD reduction**
  - CPD reduction may be reported as both **binary** and **continuous** outcome
  - Where a binary outcome is used, provide justification for threshold used for coding

# COHORT STUDY CONSIDERATIONS: STATISTICAL ANALYSES

- FDA has reviewed both **descriptive** and **inferential** analyses to evaluate findings
- Regression analyses can be used to address:
  - Repeated measures
  - Confounders
  - Any sensitivity analyses
- FDA reviews results for **internal validity** such as:
  - Robust across various model specifications
  - Consistent over the study duration and with the recruitment methods used
- FDA reviews for explanations of how **missing data** or **loss to follow-up** were addressed such as:
  - Describe approaches used for imputation of missing data or analyses of missingness

# APPH

- My goal for today was to illustrate how a couple of the key factors of risk and benefit fall along a continuum, illustrating why getting to APPH is not a simple checklist or formula
- Our intention is to continue to elaborate on our thinking around APPH in the coming months to increase transparency in our decision making
- Some of you may have also noticed that we have recently released more scientific memos on the FDA website