Human Abuse Liability Assessment of Tobacco and Nicotine Products: Considerations to Meet Current Regulatory Recommendations*

- Andrea Vansickel (Altria Client Services LLC)
- Sarah Baxter (RAI Services Company)
- Neil Sherwood (Independent Consultant)
- Leanne Campbell (RAI Services Company)
- Michael Kong (Altasciences Clinical Research)

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Abuse Liability (AL)

“Abuse liability refers to the potential of a substance to result in addiction and be used repeatedly or even sporadically resulting in undesirable effects.”

U.S. Department of Health and Human Services, Food and Drug Administration. 21 CFR Parts 1100, 1107, and 1114. [Docket No. FDA–2019–N–2854] RIN 0910–AH44. Premarket Tobacco Product Applications and Recordkeeping Requirements. Federal Register/Vol. 84, No. 186/Wednesday, September 25, 2019/Proposed Rules

Regulatory bodies recommend including information on AL to inform product authorization

Regulatory/Authoritative Body	Regulatory Guidance/Recommendation
World Health Organization **(WHO)** – Study group on Tobacco Product Regulation **(TobReg)**	Relationship of tobacco product contents and design features to dependence potential and consumer appeal
United States Food and Drug Administration **(US FDA)** Pre-Market and Modified Risk Tobacco Product Applications	"*FDA proposes to require the submission of abuse liability information…If FDA lacks sufficient information regarding the potential abuse liability of the new tobacco product, it intends to issue a no marketing order for the new tobacco product.*"*
European Union Scientific Committee on Emerging and Newly Identified Health Risks **(SCENIHR)**	Enhanced reporting for 15 priority list tobacco ingredients, including information on their addictiveness
WHO Framework Convention on Tobacco Control **(FCTC)**	Implemented laws to regulate features of tobacco products, such as flavors, and to address issues surrounding attractiveness and addictiveness

Premarket Tobacco Product Applications and Recordkeeping Requirements. Federal Register/Vol. 84, No. 186/Proposed Rules

Key considerations for New Drug Applications can be applied to tobacco products

Study Site

- Performed in either an inpatient or outpatient setting
- Subjects screened for drugs of abuse
- Medical personnel available for potential Adverse Events (AEs)

Subjects and Sample Size

- Studies conducted in subjects with a recent history of using products in the same pharmacological class (Tobacco/Nicotine products)
- Product use history collected
- Subjects recruited to represent races and sexes
- Sample size determined using a power analysis (powered to detect differences in primary endpoints)
- Statistical analysis based on completers (evaluable endpoints)

Food and Drug Administration Guidance for Industry, Assessment of Abuse Potential of Drugs; January 2017

Key considerations for New Drug Applications can be applied to tobacco products

Study Design

- **Randomized, double-blind (if possible), controlled, crossover study**
- **Study products should include (if possible):**
  - Placebo (or negative-control)
    - 0% nicotine product or a product with low AL (NRT)
  - 1-2 doses* of a positive control
    - Product with high AL (combustible cigarettes)
  - At least 3-doses* of the test product
  - Market comparator products may be considered

**Dose is used in pharmaceutical studies to indicate the amount of drug administered at a time. For tobacco studies, 'dose' may reflect different nicotine levels, increased # of puffs, increased duration of use, increased # of units*

- **Subjects report a favorable subjective response (e.g., increased liking, satisfaction, want to use again, relief of withdrawal symptoms) to a positive control**
  - Positive control is distinguishable from a placebo or negative control
  - Positive control product should be pharmacologically similar to the test product

Food and Drug Administration Guidance for Industry, Assessment of Abuse Potential of Drugs; January 2017

Key considerations for New Drug Applications can be applied to tobacco products

Study Design (cont.)

- **Product use considerations include:**
  - Subjects may be trained on product use (Acclimation Period)
  - Each study product should be delivered once, based on a Williams design (to balance variance, minimize carryover effect, and minimize sample size)
  - Doses* should be based on the highest proposed dose* and 2- to 3- times that level (if safe)
  - Product administration conditions should reflect a unit of use and should consider the route of administration for test conditions
  - *Ad libitum* use conditions can inform subjective experience and nicotine delivery under actual use scenarios
  - Washout (abstinence) period to ensure adequate elimination between test sessions

**Dose is used in pharmaceutical studies to indicate the amount of drug administered at a time. For tobacco studies, 'dose' may reflect different nicotine levels, increased # of puffs, increased duration of use, increased # of units*

Food and Drug Administration Guidance for Industry, Assessment of Abuse Potential of Drugs; January 2017

Key considerations for New Drug Applications can be applied to tobacco products

Study Design (cont.)

- **Timing of data collection should include onset and offset of product effects**
- **Address potential impact of other consumptive behaviors (e.g., food, caffeine, concomitant medication) on product absorption and outcome measures**
- **AL of tobacco products is driven by nicotine and its pharmacological effects**
  - Flavors have not been shown to substantially impact AL but may impact some subjective and behavioral effects, such as product liking and consumption patterns
  - Researchers should consider potential regulatory concerns around product ingredients when designing studies

Food and Drug Administration Guidance for Industry, Assessment of Abuse Potential of Drugs; January 2017

Key considerations for New Drug Applications can be applied to tobacco products

Outcome Measures

- **Pharmacokinetic (PK) Data**
  - Drug (nicotine) blood PK assessment throughout the test session
  - Correlate PK to subjective and physiological measures
- **Subjective Measures**
  - Timing of collecting the measures is based on the PK of the test product
  - Subjective Measures collected (visual analogue scale [VAS]) at specified timepoints following product administration
    - Primary measure – Primary Subjective Measure (e.g. Product Liking [similar to 'Drug Liking' from FDA guidance], Satisfaction, etc.)
    - Secondary measures – Overall Product Liking, Take Product Again, Product Similarity, Craving/Urge for a Cigarette (Urge to Smoke), and other subjective measures
- **Physiological Measures**
  - Heart rate, blood pressure

Food and Drug Administration Guidance for Industry, Assessment of Abuse Potential of Drugs; January 2017

Key considerations for New Drug Applications can be applied to tobacco products

Outcome Measures (cont.)

- **Safety Measures**
  - Clinical laboratory parameters, vital signs, electrocardiogram, oxygen saturation
  - Screen to ensure enrollment of generally healthy subjects
- **Adverse Events**

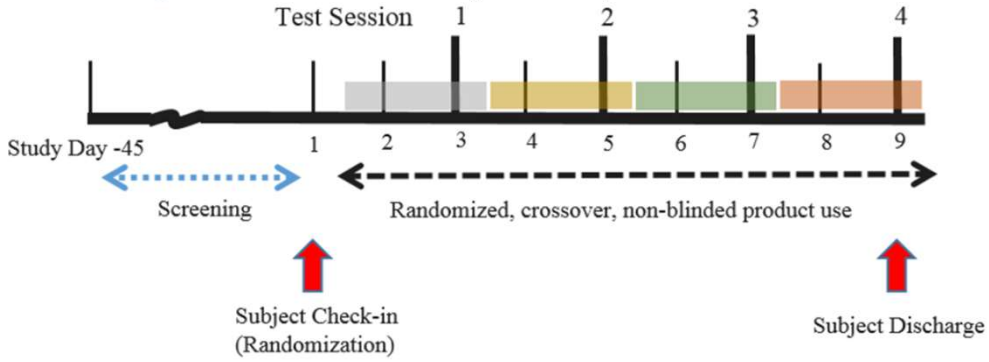
Statistical Analysis

- **Abuse-related response of the Positive Control vs. Negative Control (Placebo)**
- **Abuse-related response of the Test Product vs. Positive and Negative Controls (Placebo)**

Food and Drug Administration Guidance for Industry, Assessment of Abuse Potential of Drugs; January 2017

Example AL Study Design

- A randomized, open-label, 4-way crossover design for two ENDS
- Enrolled subjects: adult cigarette smokers 21+
- ENDS included 2 different nicotine strengths
- 9-day confinement study with 4 study product acclimation periods (1.5 days each) and 4 test sessions (4 hours each)
- Randomized product use sequence per Williams design
- 1 of 4 study products used per Test Session
  - Combustible cigarette (CC; High AL comparator)
  - ENDS 1 & 2 (Test Products)
  - NRT (nicotine gum, Low AL comparator)



Example AL Study Outcome Measures

- **Subjective Measures**
  - Direct Effects of the Product (e.g., Liking, Satisfaction), Tobacco Withdrawal

EXAMPLES

Direct Effects of Product Questionnaire

Not at All — Extremely

100 mm

1. Is the product "Pleasant" right now
2. Is the product "Satisfying" right now
3. Is the product making you feel "Calm" right now
4. Is the product helping you "Concentrate" right now
5. Is the product making you feel more "Awake" right now
6. Is the product making you feel "Sick" right now?
7. Is the product reducing your "Hunger" for food right now?
8. Would you like "More" of the product right now?

Tobacco/Nicotine Withdrawal Questionnaire

Not at All — Extremely

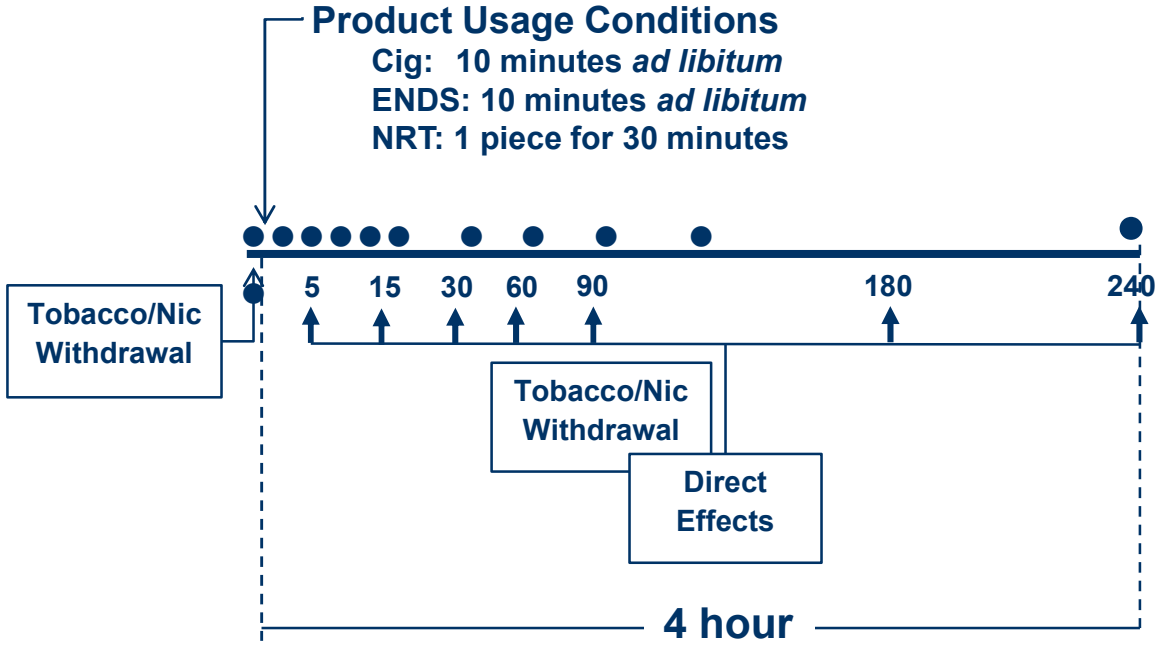
100 mm

These phrases may or may not describe how you feel right now. Please respond to each word or phrase with how you feel RIGHT NOW by drawing a vertical mark anywhere along the horizontal line.

1. Urges to smoke
2. Anxious
3. Difficulty Concentrating
4. Impatient
5. Craving a Cigarette

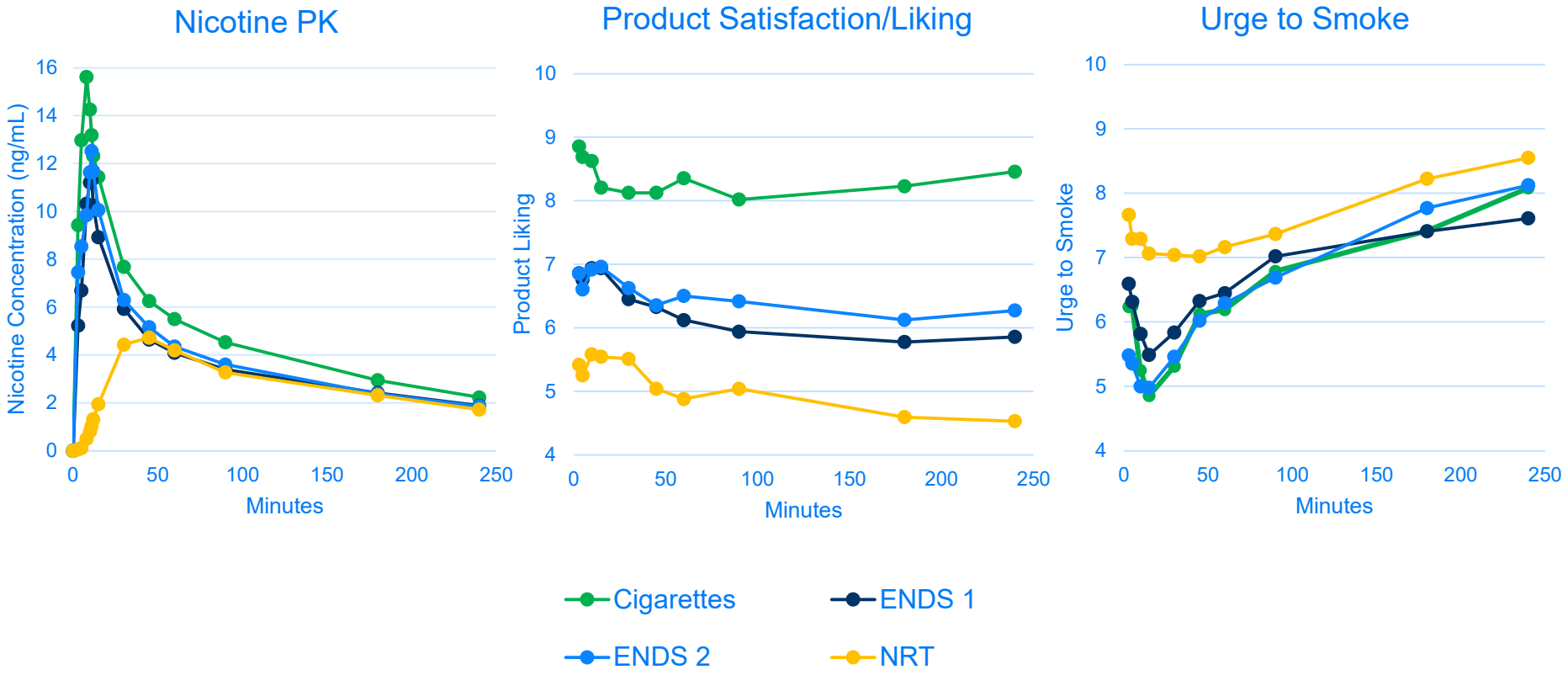
- **Nicotine Pharmacokinetics**
  - C_{max}, AUC, T_{max}
- **Vital Signs**
  - Heart Rate, Systolic and Diastolic Blood Pressure
- **Adverse Events**
  - Reported and observed

Example AL Study Events Timeline



- blood draw at 5 minutes prior to and at 2, 5, 10, 12, 15, 20, 30, 45, 60, 90, 180, and 240 minutes following the start of the product use

Example AL Study Data (Hypothetical)



TPL review findings highlight potential interpretations by FDA CTP

PK profiles and subjective effects are important for evaluating abuse liability (AL) of tobacco products

Study Findings	FDA Interpretation
More **rapid** and **higher nicotine delivery** relative to positive control (high AL product)	• Higher AL • More rapid suppression of withdrawal symptoms
Slower and **lower nicotine delivery** relative to positive control (high AL product)	• Lower AL
Lower positive **subjective effects** relative to positive control (high AL product)	• Reduced AL for nonsmokers; information was extrapolated to youth
Similar nicotine delivery and subjective effects relative to positive control (high AL product)	• Similar AL
AL Assessment Outcome	**FDA Interpretation**
Lower AL	• Reduced substitutability (lower likelihood adult smokers will switch completely)
Similar AL (nicotine delivery and subjective measures similar to positive controls)	• Potential benefit for smokers trying to switch • AL risk no greater than currently available tobacco products

Submissions evaluated include:

- **22nd Century Group, Inc. for Moonlight (VLNC) Cigarettes**
- **Swedish Match North America, Inc. for Loose and Portioned Snus**
- **Philip Morris Products S.A. for IQOS® and Marlboro Heatsticks®**

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Please direct questions to:

Andrea Vansickel
Sr. Principal Scientist, Regulatory Science
Altria Client Services LLC
Andrea.R.Vansickel@altria.com