Challenges and Considerations Related to Human Abuse Liability Testing for Tobacco Products:

Opportunities to Establish Tobacco-Specific Methods, Measures, and Evaluation Criteria

February 13th, 2023

- Andrea Vansickel (Altria Client Services LLC)
- Sarah Baxter (RAI Services Company)

- This presentation includes the output of the CORESTA Product Use Behavior Subgroup (NWIP 156)

Agenda

- **Part One: Abuse Liability (AL) Testing Strategies for Tobacco Products**
  - Sarah Baxter
- **Part Two: Challenges and Opportunities for Future Studies**
  - Andrea Vansickel

Regulatory bodies leverage AL data 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	"Section 1114.7(k)(1)(ii)(A) requires a PMTA to contain full reports of investigations into the abuse liability of 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. 86, No. 190/Rules and Regulations

CORESTA Recommendations for AL Assessment of Tobacco Products

Nicotine & Tobacco Research, 2022, 295–305
https://doi.org/10.1093/ntr/ntab183
Review
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SRNT OXFORD

Review

Human Abuse Liability Assessment of Tobacco and Nicotine Products: Approaches for Meeting Current Regulatory Recommendations

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Abstract

Many regulatory bodies now recommend that tobacco product manufacturers provide information regarding new tobacco products' abuse liability to inform regulatory authorization of currently marketed tobacco products or new product applications (including premarket tobacco product applications in the United States). In addition, the US Food and Drug Administration (FDA) recommends including this information as part of modified risk tobacco product applications. Regulators, including FDA, and many public health officials and researchers consider abuse liability assessment a model which predicts the likelihood that the use of the tobacco product would result in addiction and be used repeatedly or even sporadically resulting in undesirable effects. Abuse liability of a new, potentially reduced harm product can also inform its ability to substitute completely for more harmful tobacco products. While many methods exist, no standard tobacco product abuse liability assessment has been established. The purpose of this review is to provide background information and practical recommendations for human abuse liability testing methods to meet tobacco regulatory needs. A combination of nicotine test product pharmacokinetic, subjective effect and/or behavioral response, and physiological response data relative to comparator products with known abuse liability satisfies some regulatory requirements

ntab183.pdf (silverchair.com)

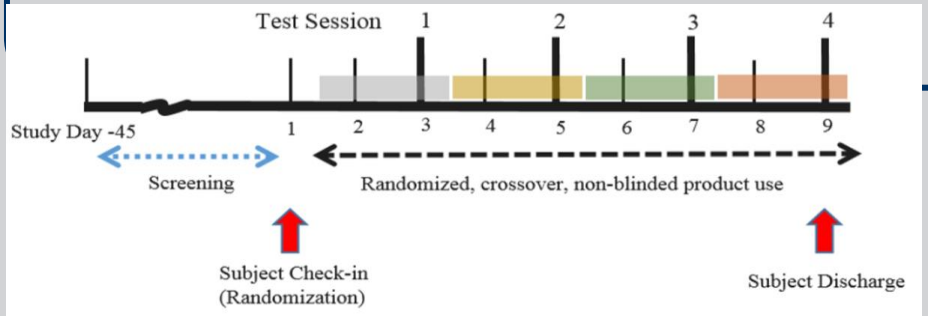
"While many methods exist, no standard tobacco product abuse liability assessment has been established."

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

Study Design Considerations

- **Randomized, double-blind (if possible), controlled, crossover study**
- **Study products:**
  - Placebo (or negative-control; NRT)
  - 1-2 doses* of a positive control (CC)
  - At least 3-doses* of the test product
  - Market comparator products may be considered
- **Subjects use each study product at least once**

**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

Outcome Measures

- **Data collected over onset and offset of product effects:**
  - **Subjective Measures**
    - **Primary subjective measure –** e.g. Product Liking [similar to 'Drug Liking' from FDA guidance], Satisfaction, etc.
    - **Secondary subjective measures –** Overall Product Liking, Use Product Again, Product Similarity, Craving/Urge for a Cigarette (Urge to Smoke), and other subjective measures
    - **Timing** is based on the PK of the test product
  - **Pharmacokinetic (PK) Data**
    - **Nicotine PK (C_{max}, T_{max}, AUC)**
  - **Physiological Measures**
    - **Heart rate, blood pressure**
  - **Safety Measures**
  - **Adverse Events**

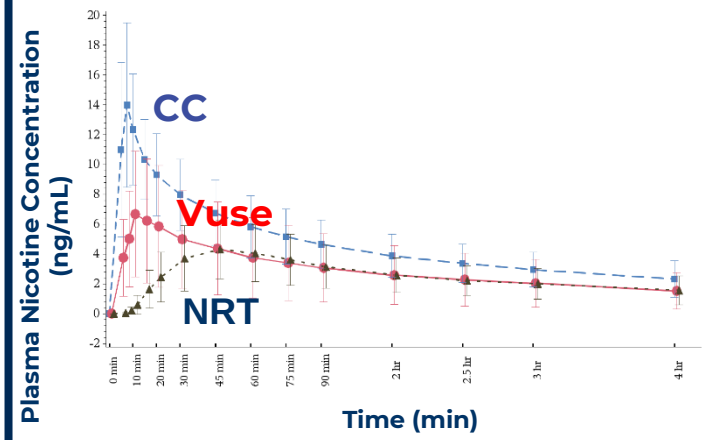
Food and Drug Administration Guidance for Industry, Assessment of Abuse Potential of Drugs; January 2017

Additional information considered for nicotine product AL assessments

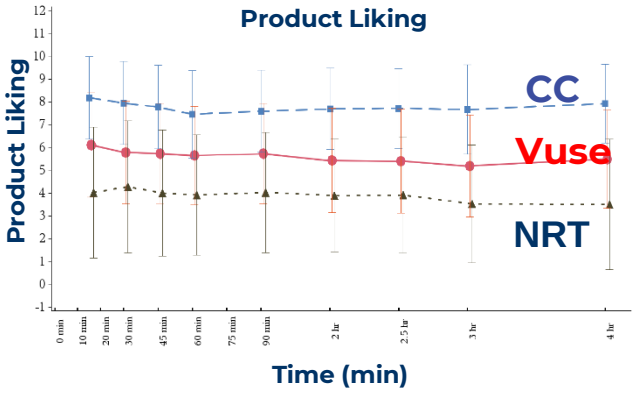
- Product use topography
- Actual use data
- Measures of exposure
- Product misuse

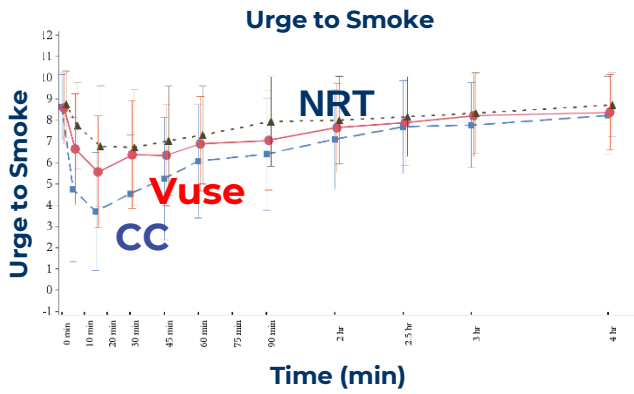
MGO Case Study: Vuse Solo

Pharmacokinetics



Pharmacodynamics





Additional data considered

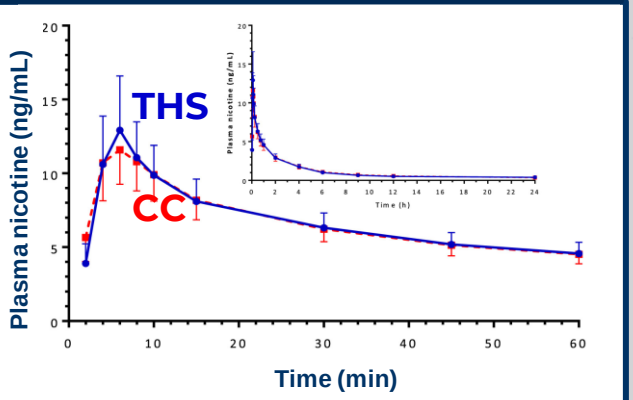
- Nicotine exposure in a 5-day exposure study

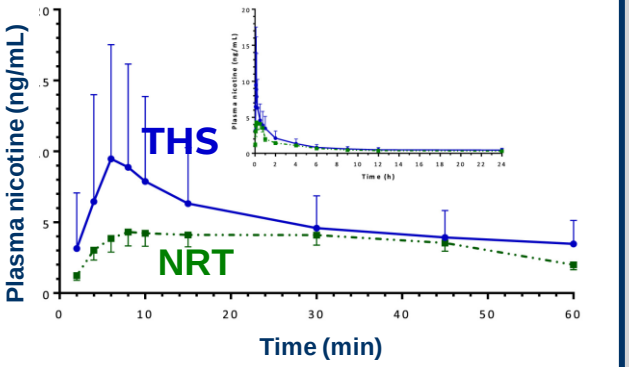
Vuse Solo AL falls between CC and NRT

Campbell et al. Sci Rep, 12, 22080 (2022)

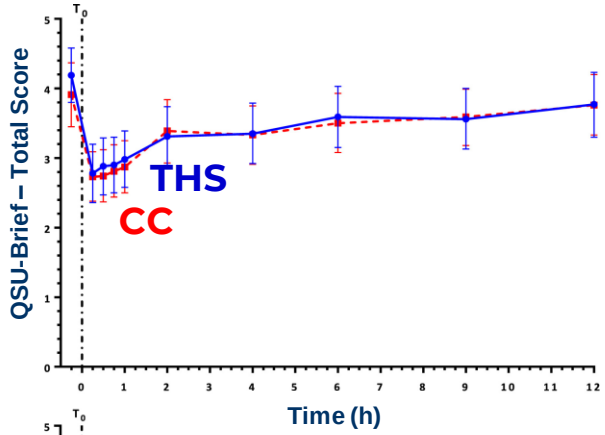
MGO Case Study: IQOS

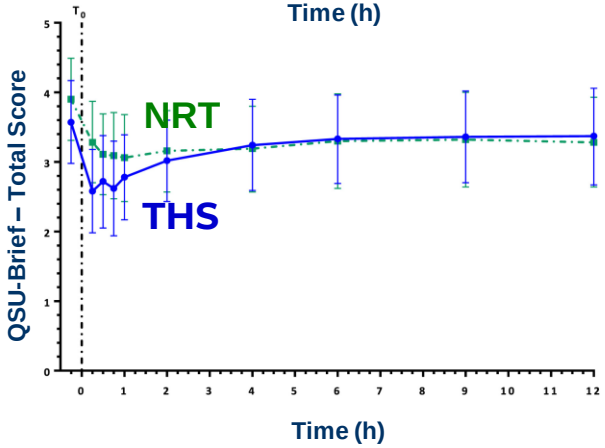
Pharmacokinetics





Urge to Smoke





Additional data considered

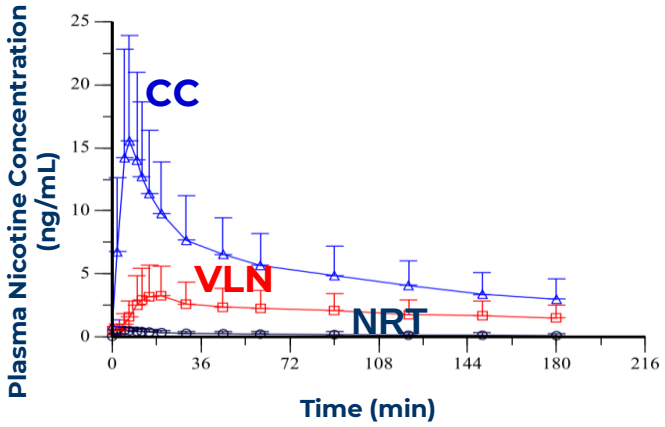
- Nicotine exposure in reduced exposure studies
- Use topography
- Additional subjective measures: withdrawal, dependence and reinforcement
- Product misuse

IQOS AL similar to CC

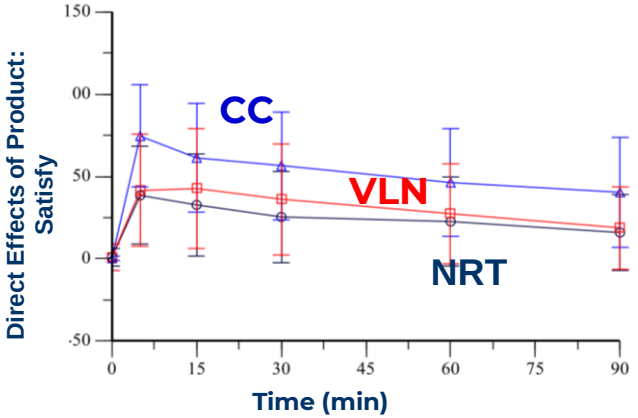
Brossard et al. Reg tox Pharm, 89 (2017)

MGO Case Study: VLN King Cigarettes

Pharmacokinetics

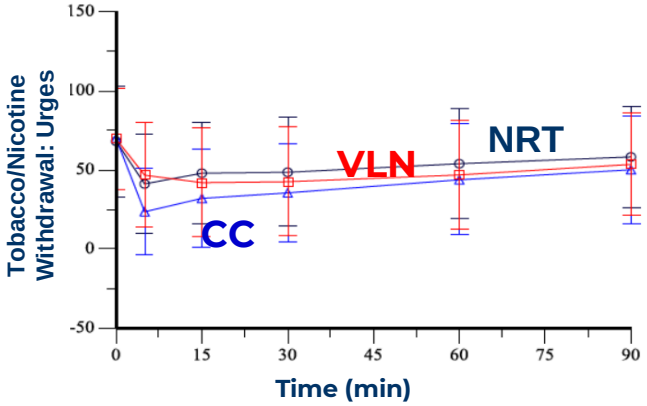


Pharmacodynamics



Additional data considered

- Use topography
- Additional subjective measures such as craving, withdrawal, product effects in acute and long-term switching studies



AL of VLN Cigarettes is lower than CC

Challenges and Opportunities for Future Studies

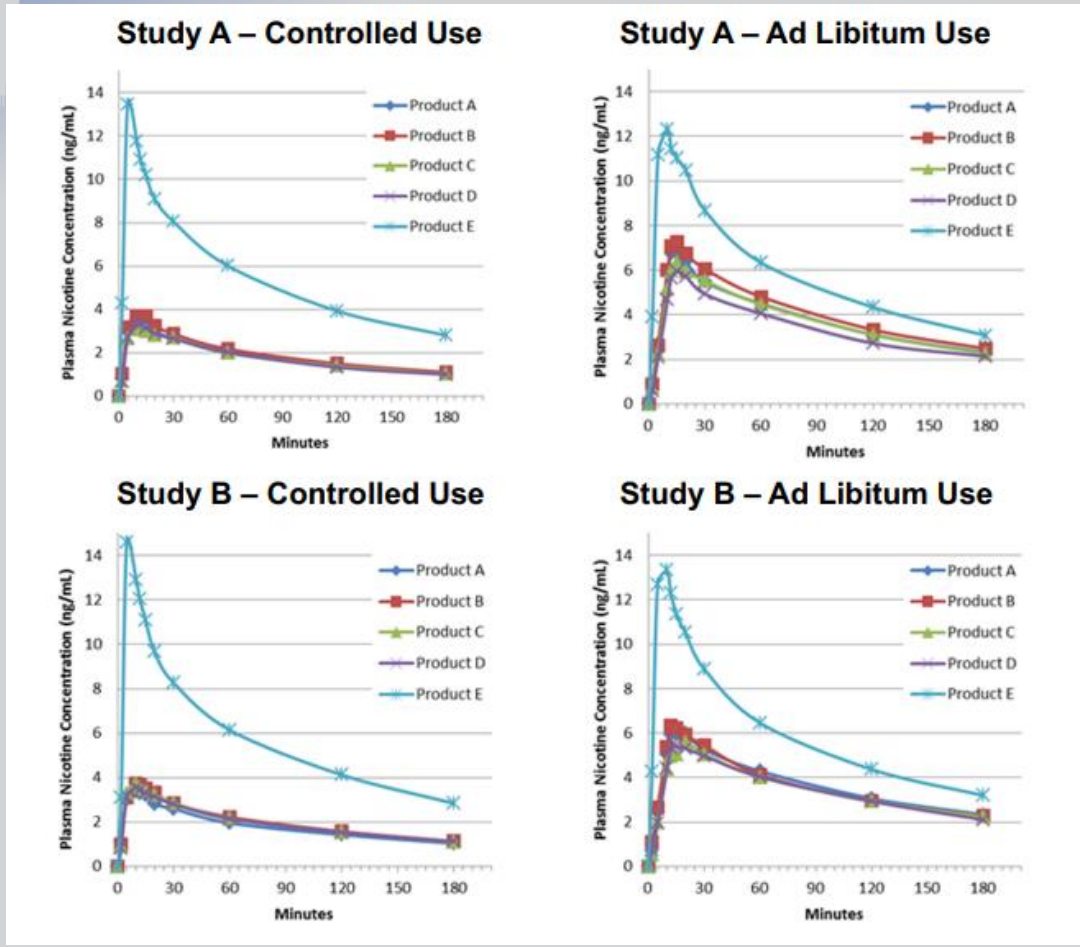
- Clinical, randomized, crossover studies involving PK and PD assessment serve as the main evaluation of AL for new and modified risk tobacco product applications – not unlike FDA review of new psychoactive drugs
- Much experience has been gained applying these traditional AL testing methods to tobacco products – that experience reveals challenges with measurement methods and data interpretation

Differences Between New Drug and New Tobacco Product Evaluation

- Market comparators may be considered for tobacco products
- Participant preferences for flavors and nicotine levels must be considered for tobacco products, they are consumer products – not intended to treat an underlying condition
- Tobacco products = same psychoactive constituent (nicotine) but different forms (e.g., oral vs. inhalable)
- Individual use patterns influence nicotine delivery, unlike many therapeutic drugs, which primarily focus on dose
- Abuse Liability testing of therapeutics to meet drug scheduling requirements vs. determining whether a new tobacco product is appropriate for the protection of public health (APPH)

CHALLENGE: Controlled Use Conditions do Not Necessarily Reflect Actual Use Patterns

Nicotine Delivery from E-Vapor Products Under Controlled (10-puff, 30s ipi) and *Ad Libitum* (10-minutes) In-Clinic Conditions

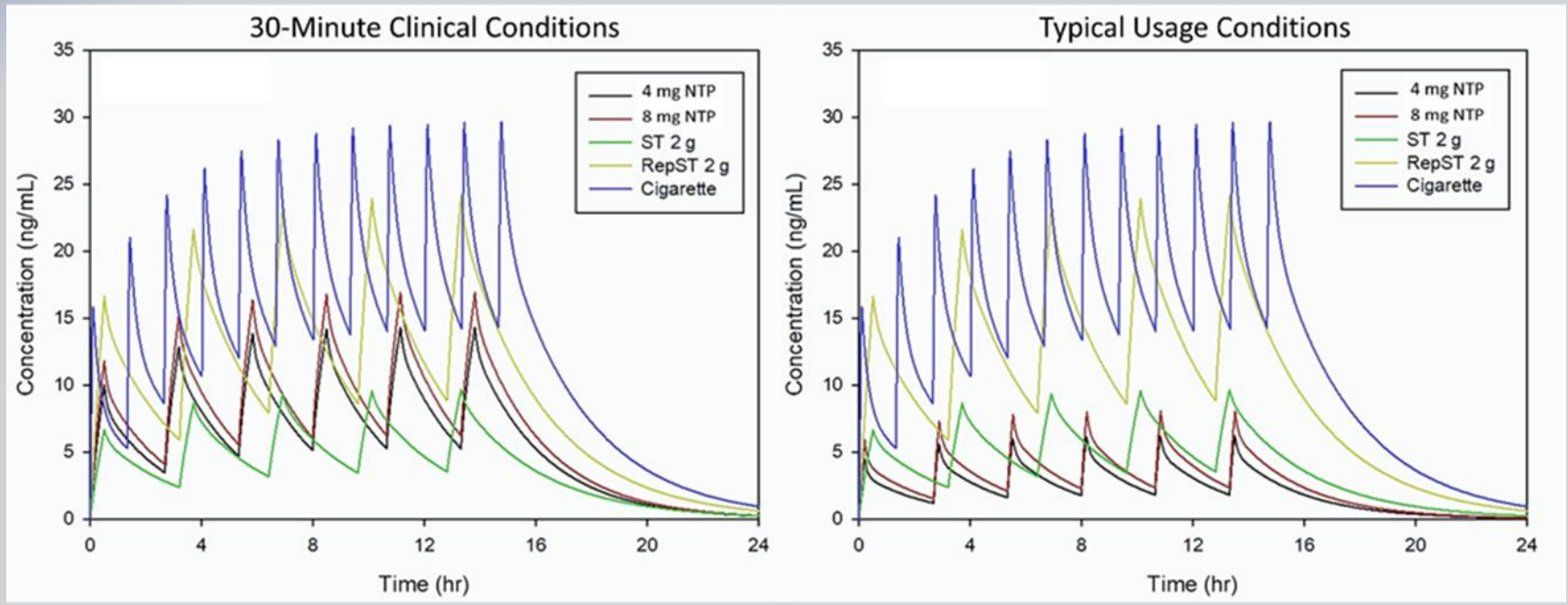


- Even under in-clinic conditions, *ad libitum* and controlled use of e-vapor products result in different nicotine delivery

Oliveri, D.; Edmiston, J.; Gogova, M.; Vansickel, A.; Wang, J.; Zhao, Y.; Sarkar, M., "Characterization of Nicotine Exposure Profiles and Subjective Measures of e-Vapor Productsin Adult Smokers Relative to Conventional Cigarettes". *Poster presented at the24th Annual Meeting of the Society for Research on Nicotine and Tobacco (SRNT), Baltimore, MD, February 21-24*, 2018. Poster

CHALLENGE: Controlled Use Conditions do Not Necessarily Reflect Actual Use Patterns

Simulated, baseline-adjusted nicotine exposure during multiple 4 and 8 mg on! nicotine pouch product uses across a 16-hour day under controlled clinical and typical, at-home usage conditions



Controlled Condition: 30-minutes in mouth

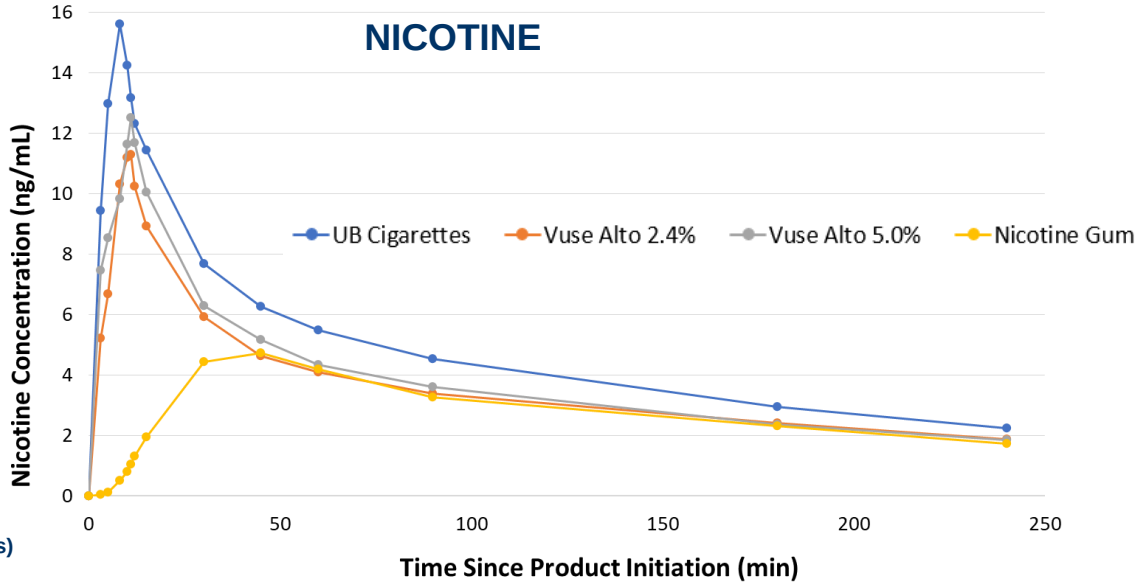
Actual Use: 12-minutes in mouth (median value)

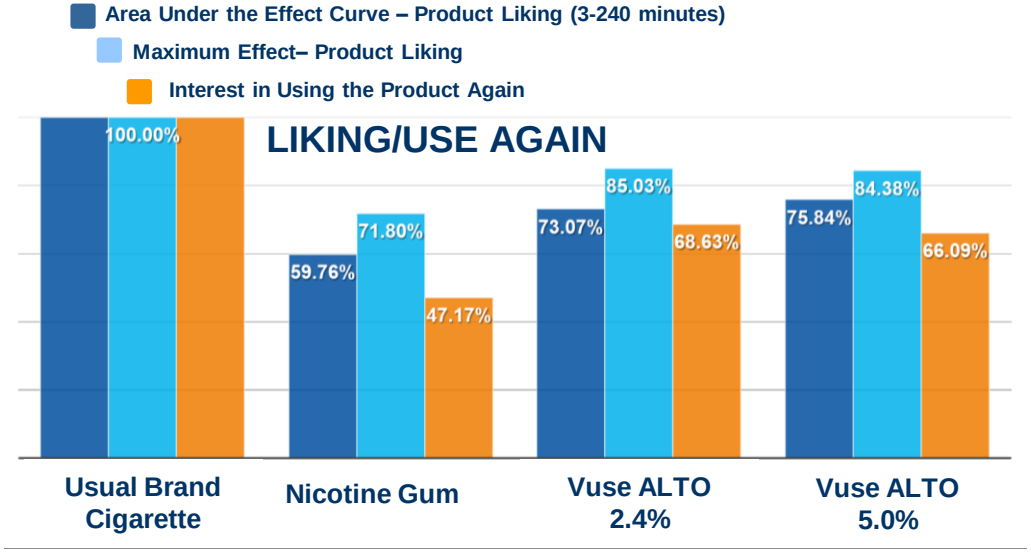
median # of pouches per day: 6; average dips per day: 5; average cigarettes per day: 12

Vansickel, A.; Nguyen, N.; Edmiston, J.; Sarkar, M., "Pharmacokinetic modeling and simulation of single and multiple uses of an oral tobacco-derived nicotine product compared to moist smokeless tobacco products and combustible cigarettes under actual use conditions.". Poster presented at the 27th Society for Research on Nicotine and Tobacco (SRNT), Virtual Conference, February 24-27, 2021. Poster

CHALLENGE: Tobacco Product Nicotine Level Does Not Necessarily Predict Nicotine Delivery Under *Ad Lib* Conditions or Drive Likelihood of Use

Nicotine delivery is similar across e-vapor products under *ad lib* conditions, despite 2-fold product nicotine level difference





Interest in using again and product liking scores similar across e-vapor products, despite 2-fold nicotine level difference

Adapted from: ABUSE LIABILITY ASSESSMENT OF VUSE ALTO ELECTRONIC NICOTINE DELIVERY SYSTEM (ENDS) AS COMPARED TO COMBUSTIBLE CIGARETTES AND NICOTINE REPLACEMENT THERAPY (NRT) IN ADULT SMOKERS. Kyung soo HONG, John Darnell, Eckhardt Schmidt, Sarah Baxter-Wright, Paul Nelson and Elaine Round; RAI Services Company, Winston[1]Salem, NC USA; 74th TSRC Aug 29-31 2021, Boston, MA

CHALLENGE: Tobacco Product Nicotine Level Does Not Necessarily Drive Likelihood of Use

Willingness to use the product again following in-clinic use among dual MST/Cig

 # Neutral or Unwilling to Use

 # Willing to Use

Product (on!® Mint)	-50 to < 0	0	> 0 to 50
1.5 mg	9	1	19
2mg	10	3	16
3.5mg	8	3	17
4mg	9	2	17
8mg	10	5	13

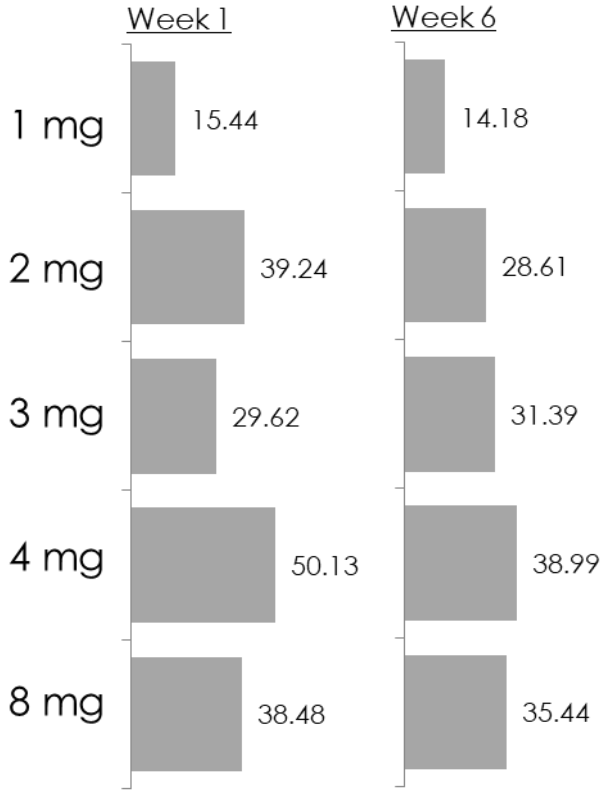
If given the opportunity, I would want to use this product again.

Definitely Would Not — Don't Care — Definitely Would

100 mm

Actual use of product during at-home, open-access, 6-week use period

% of Adult Dual Users of MST and Cigarettes Reporting Use of Each on! Nicotine Strength: 6-Week Actual Use Study

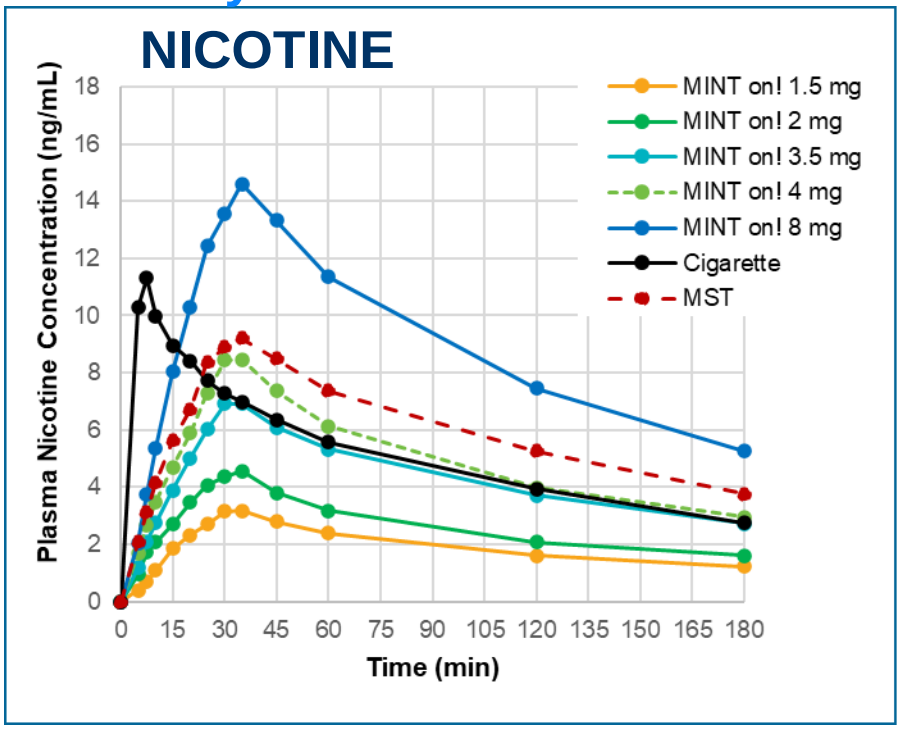


Nicotine pharmacokinetics and subjective responses after using nicotine pouches with different nicotine levels compared to combustible cigarettes and moist smokeless tobacco in adult tobacco users - PMC (nih.gov)

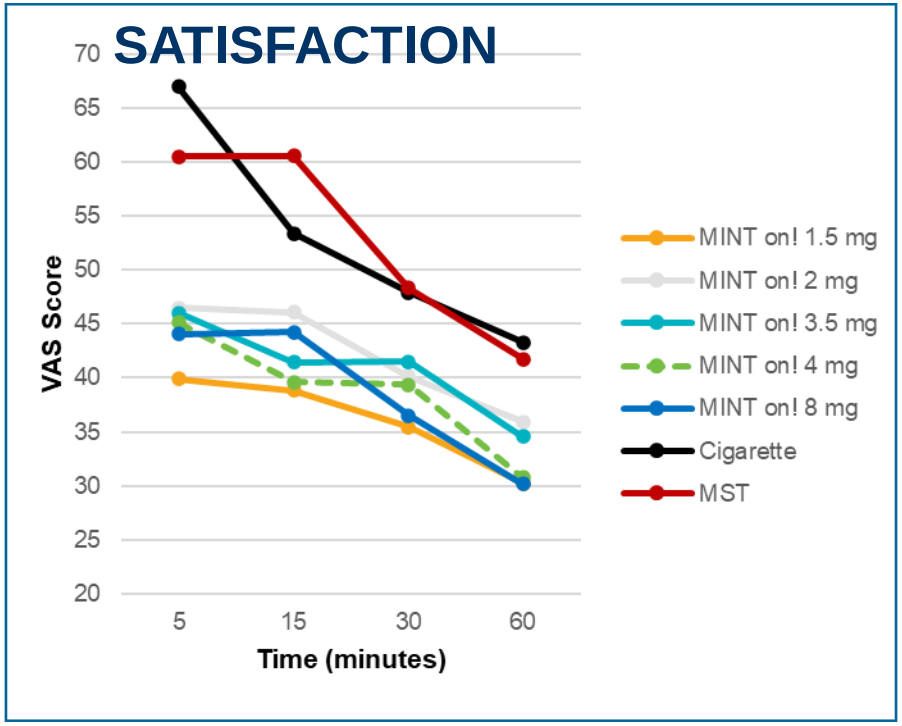
Results of ALCS on! 6-week Actual Use Study

CHALLENGE: Existing Subjective Measures are not Sensitive Enough to Detect Differences in Nicotine Effects Within Product Category

Clear distinction in nicotine delivery across nicotine levels



No distinction in satisfaction ratings across nicotine levels

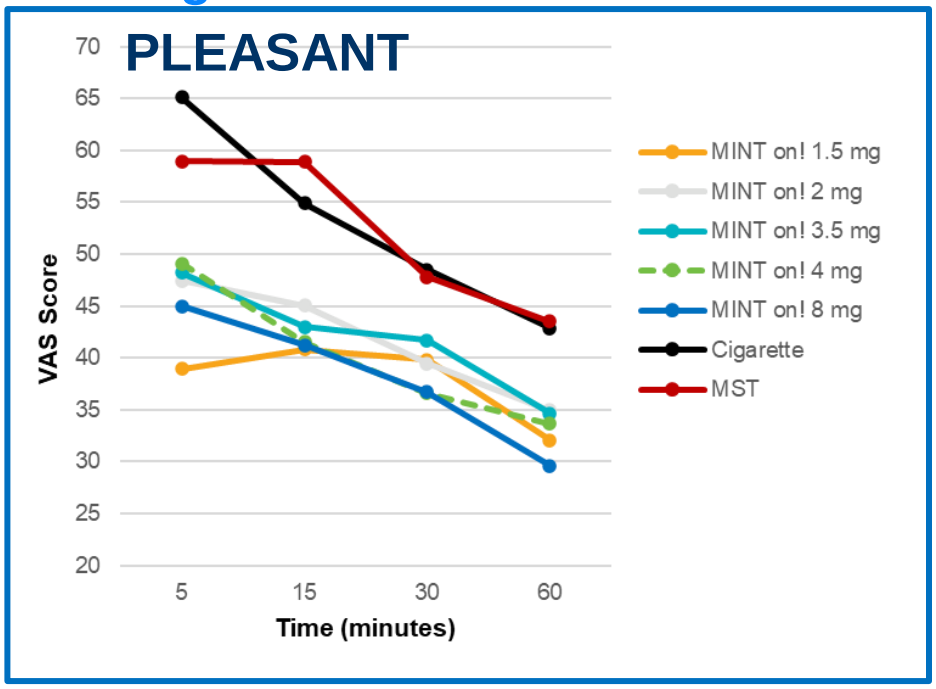


VAS = Visual Analog Scale

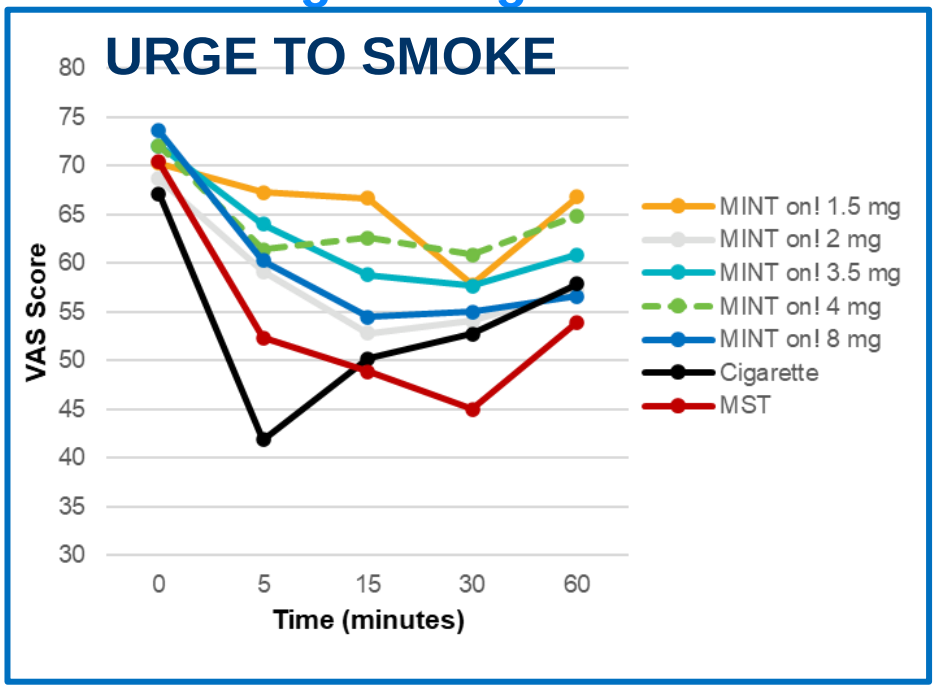
Nicotine pharmacokinetics and subjective responses after using nicotine pouches with different nicotine levels compared to combustible cigarettes and moist smokeless tobacco in adult tobacco users - PMC (nih.gov)

CHALLENGE: Existing Subjective Measures are not Sensitive Enough to Detect Differences in Nicotine Effects Within Product Category

No distinction in pleasant ratings across nicotine levels



No clear nicotine response on ratings of urge to smoke



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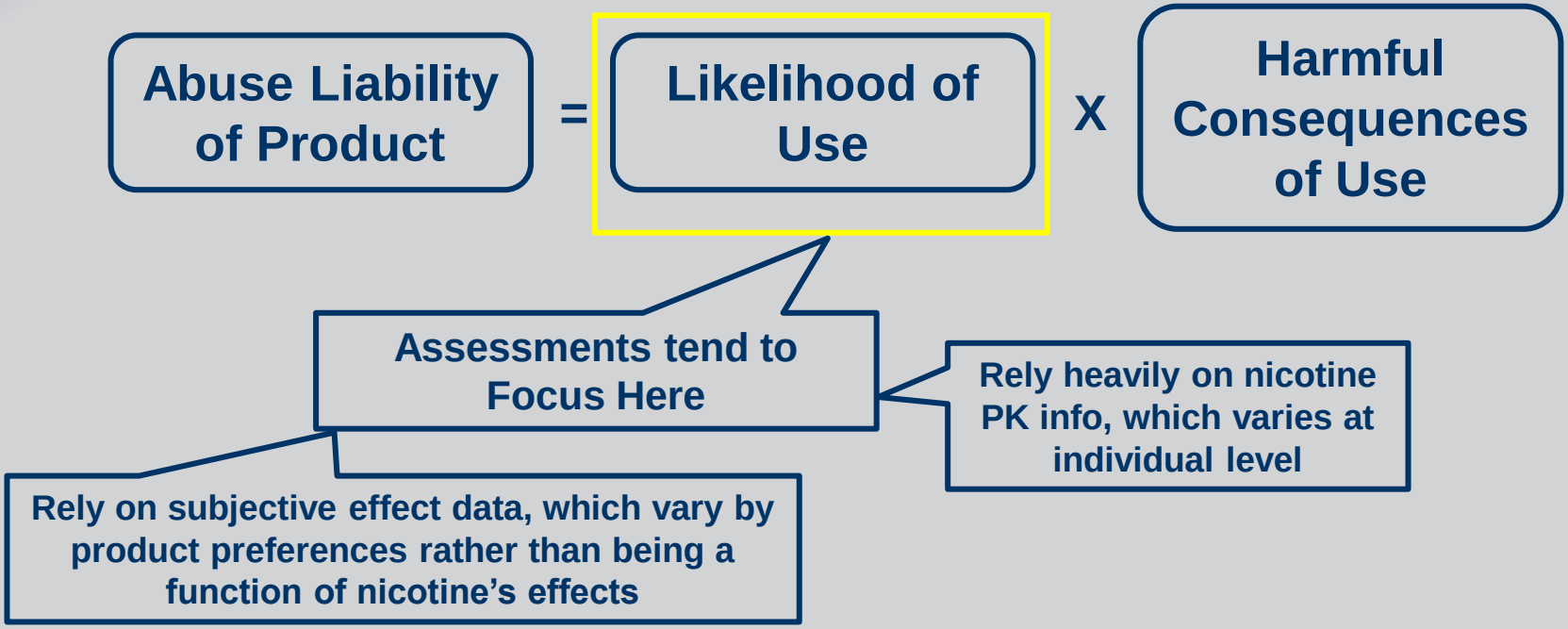
Opportunities: Abuse Liability Assessment of Tobacco Products

"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. 86, No. 190/Tuesday, October 5, 2021/Rules and Regulations*

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®**

Opportunities: Abuse Liability Assessment of Tobacco Products

- Existing methods and measures for AL testing successfully distinguish between tobacco product categories with differing routes of administration and product characteristics, but not within product categories
- Evidence from this type of testing provides critical information for FDA's evaluation of whether a product is APPH
- There are opportunities to streamline and evolve existing measures to better isolate abuse liability-related effects from consumer product preferences within complex tobacco product categories
- There are also opportunities to mature the way we interpret abuse liability-related information by examining the information in the broader context of individual and overall public health

Acknowledgements

- Neil Sherwood (Independent Consultant)
- Leanne Campbell (RAI Services Company)
- Michael Kong (Altasciences Clinical Research)

- Krishna Prasad (British American Tobacco)
- Xavier Cahours (Imperial Tobacco Limited)
- CORESTA PUB Subgroup

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