Assessing Tobacco Product Abuse Liability in the Context of the APPH Standard

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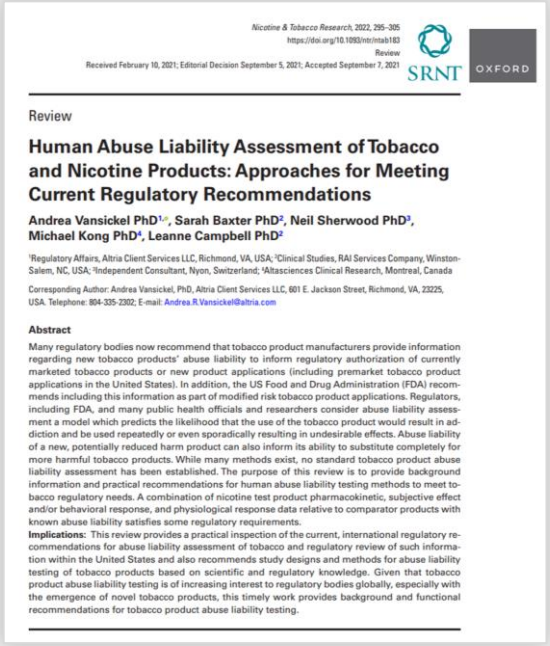
Tobacco Human Abuse Liability (AL) Guidance



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Review
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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.

Implications: This review provides a practical inspection of the current, international regulatory recommendations for abuse liability assessment of tobacco and regulatory review of such information within the United States and also recommends study designs and methods for abuse liability testing of tobacco products based on scientific and regulatory knowledge. Given that tobacco product abuse liability testing is of increasing interest to regulatory bodies globally, especially with the emergence of novel tobacco products, this timely work provides background and functional recommendations for tobacco product abuse liability testing.

1

FDA GUIDANCE[2]

AL Definition

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

Investigations that Inform AL

"including data regarding product **chemistry, pharmacology,** and **pharmacokinetic** characteristics."

Clinical AL Study Design

"The 'standard' abuse liability study is a double-blind, placebo-controlled, within-subject study comparing several doses of a new product to a comparator product with a known abuse liability. Generally, the **primary outcome measure is peak 'liking'** (Emax) as reported via a visual analog scale"

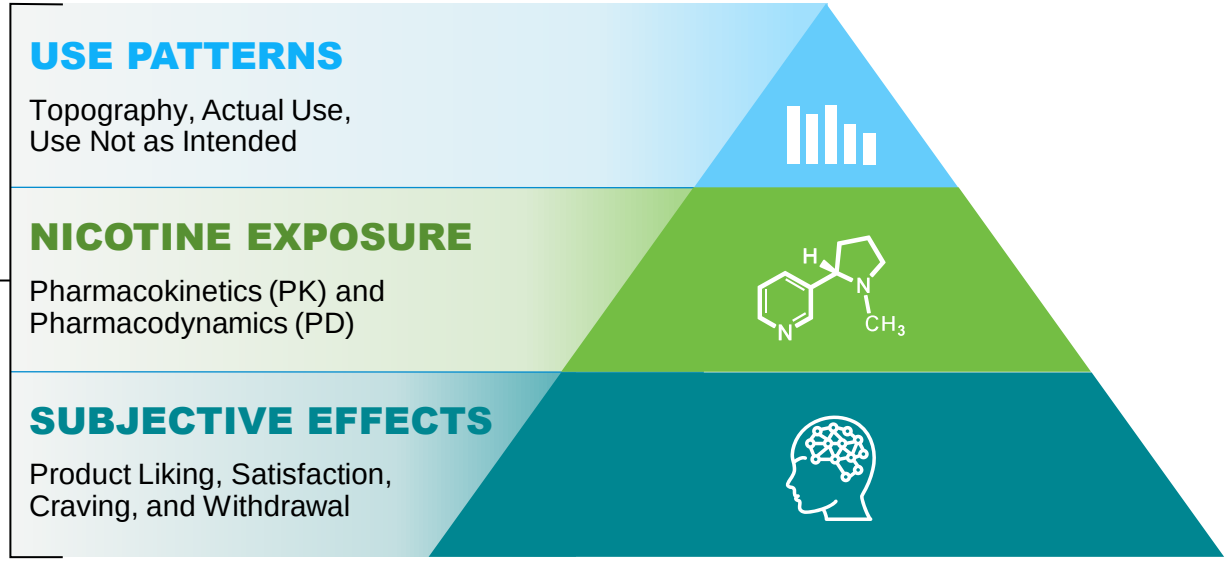
1. https://pubmed.ncbi.nlm.nih.gov/34498698/
2 2021-21011.pdf (govinfo.gov)

TYPICAL Tobacco AL Framework

The typical AL assessment has been acceptable to FDA: Market authorizations granted for Verve®, IQOS®, NJOY®, Vuse®, VLN™, etc.

Relative to other tobacco/nicotine products with known AL

Standard AL studies successfully distinguish between product categories (e.g. cigarette vs. e-vapor)



PD=nicotine pharmacodynamics; PK=nicotine pharmacokinetics.

FDA – Current Thinking on AL and APPH

AL Evaluation Should Inform:

- Substitutability of new/modified risk product
- Likelihood of initiation & use progression

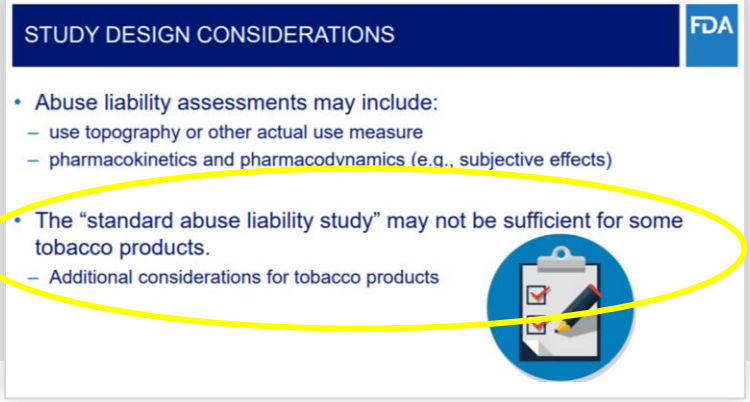
AL Evaluation May Include:

- Information on patterns of use
- Nicotine pharmacokinetics (PK) and pharmacodynamics (PD)

ABUSE LIABILITY & PUBLIC HEALTH STANDARD

FDA

- "People smoke for nicotine, but they die from the tar." – Michael Russell
- Informs the likelihood that addicted users of one nicotine product would switch (e.g., dual use, exclusive use) to another.
- Informs the likelihood that new users of a product will progress to regular use.
- If a new product has a high abuse liability, current addicted tobacco users interested in quitting may find it to be an adequate substitute for the product they are currently using. On the other hand, low abuse liability makes it less likely that new users will become addicted.



AL=abuse liability.

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While the typical AL evaluation framework has been accepted by FDA, there are some limitations to address

Results of standard AL studies do not reflect real world usage conditions

- **Individual differences in use patterns**
- **Consumer product preferences**

In-clinic conditions **do not necessarily reflect nicotine exposure under actual usage conditions** (varying use patterns, individual characteristics, tobacco-naïve)

Subjective assessments (PD) **do not always align with nicotine delivery** (other sensory attributes of tobacco products)

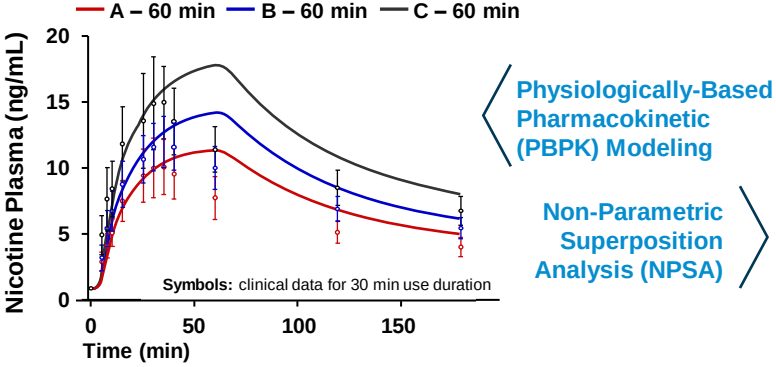
In-clinic nicotine delivery and subjective responses **do not always predict use in the real world**

In-clinic Conditions Do Not Reflect Actual Use Patterns and Resulting Nicotine Exposure – Modeling Tools Can Help

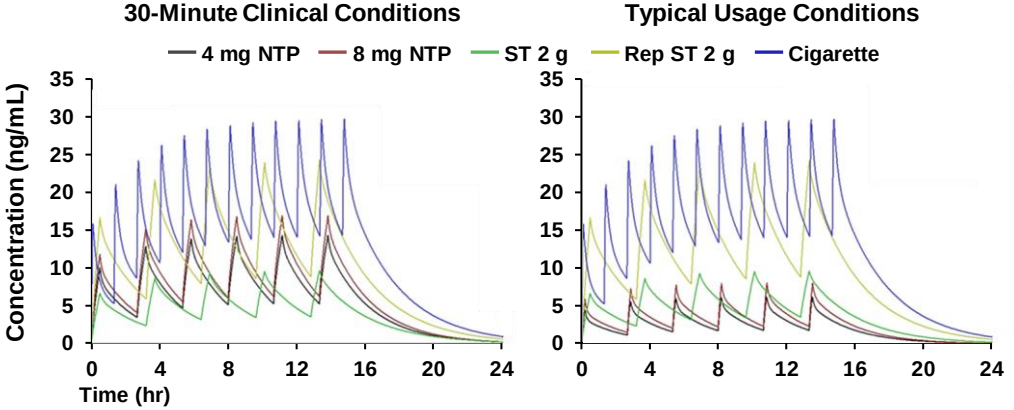
Modeling Use Case Scenarios

- Duration of use
- Amount of use
- Multiple products at the same time
- Varying nicotine contents of products
- Multiple usages over time

PBPK is superior to NPSA in terms of predictability but requires more inputs



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

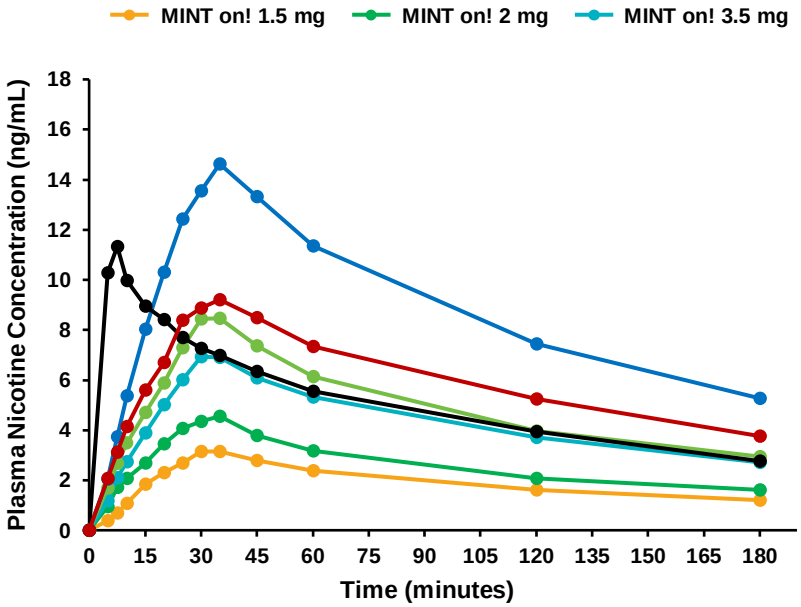


MEDIAN # OF POUCHES PER DAY: 6; Time in Mouth: 12-minutes; MEAN DIPS PER DAY: 5; MEAN CIGARETTES PER DAY: 12

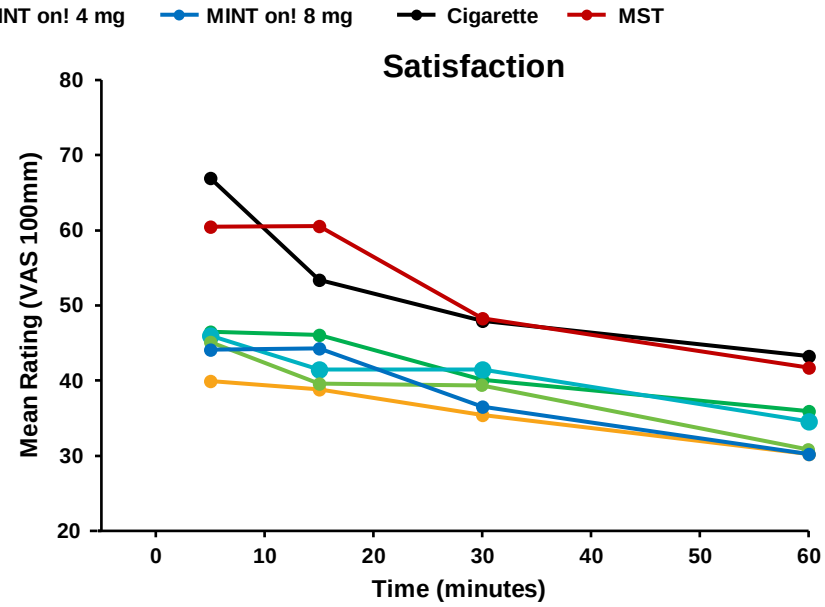
A comprehensive physiologically based pharmacokinetic (PBPK) model for nicotine in humans from using nicotine-containing products with different routes of exposure - PMC (nih.gov)

Subjective Ratings in the Clinical Setting Do Not Always Align with Nicotine Delivery

Clear Distinction in Nicotine Delivery Across Nicotine Levels



No Distinction in Satisfaction Ratings across Nicotine Levels

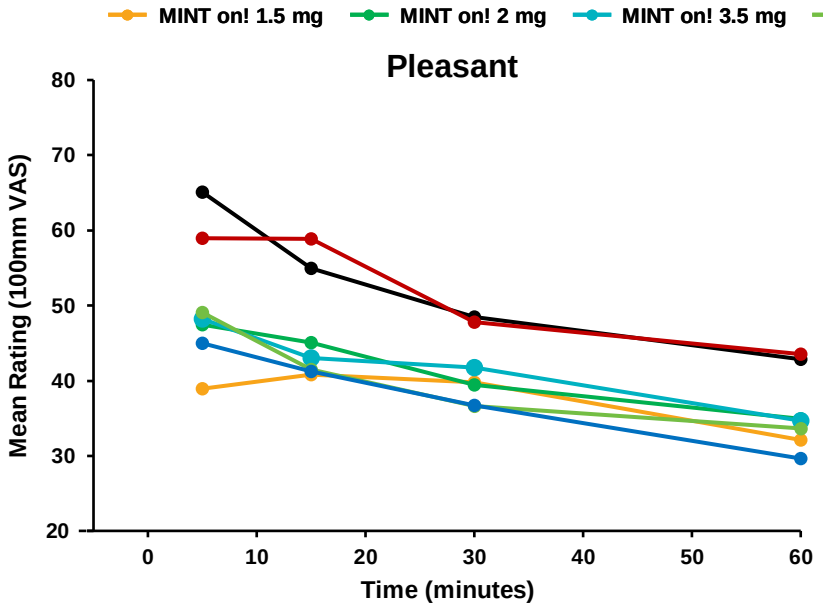


VAS=Visual Analog Scale.

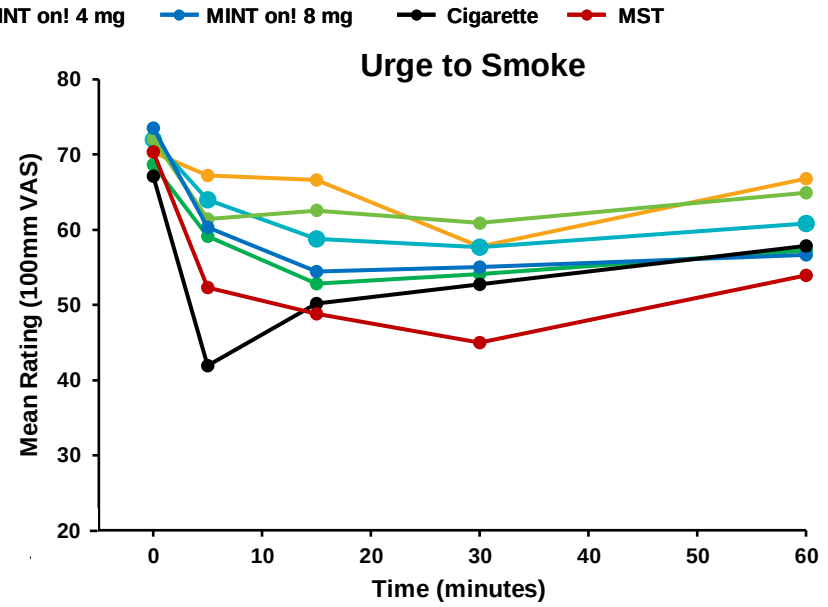
Nicotine pharmacokinetics and subjective responses after using nicotine pouches with different nicotine levels compared to combustible cigarettes and moist smokeless tobacco in adult tobacco users - PMC (nih.gov)

Subjective Ratings in the Clinical Setting Do Not Always Align with Nicotine Delivery

No Distinction in Pleasant Ratings Across Nicotine Levels



No Clear Nicotine Response on Ratings of Urge to Smoke



MST=moist smokeless tobacco; 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)

In-clinic Nicotine Delivery and Subjective Ratings Do Not Always Predict Use Patterns in the Real World

Willingness To Use The Product Again Following In-clinic Use Among Dual MST/Cig[1]

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

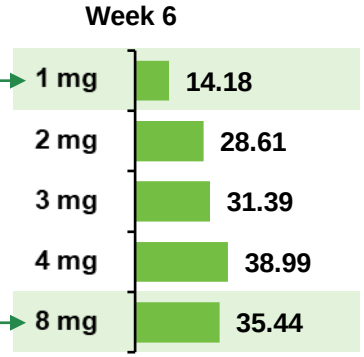
If given the opportunity, I would want to use this product again.

DEFINITELY WOULD NOT — DON'T CARE — DEFINITELY WOULD

100 mg

Actual Use of Product During At-home, Open-access, 6-week Use Period[2]

% of Adult Dual Users of MST and Cigarettes Reporting Use of Each on!® Nicotine Strength



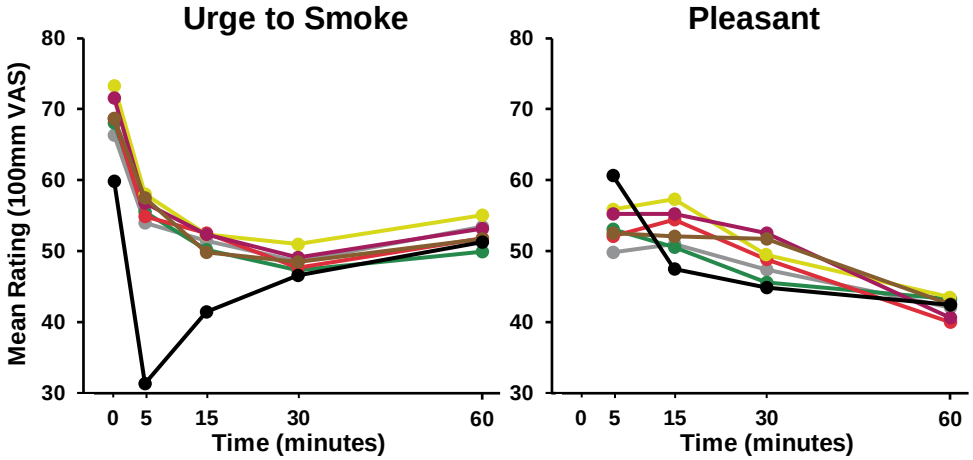
Note: The 1.5 and 1 mg and the 3.5 and 3 mg nicotine pouches were the same products – the nicotine level descriptions were updated upon further analytical testing, but we stayed true to the descriptions used in study documentation

MST=moist smokeless tobacco.

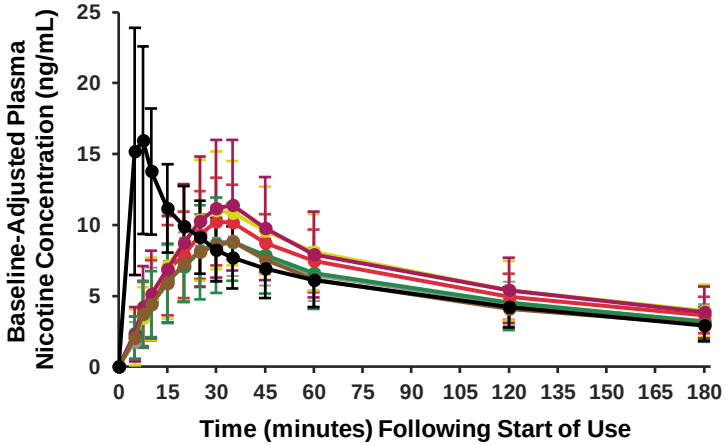
1. Nicotine pharmacokinetics and subjective responses after using nicotine pouches with different nicotine levels compared to combustible cigarettes and moist smokeless tobacco in adult tobacco users - PMC (nih.gov)
2. Characterization of Ad Libitum Use Behavior of On! Nicotine Pouch...: Ingenta Connect

In-clinic Data Show No Difference in AL Across Flavors with Same Nicotine Content – Data do not Reflect Preference

No Difference in Pleasant or Urge to Smoke Ratings Across Flavors



No Difference in Nicotine Delivery Across Flavors

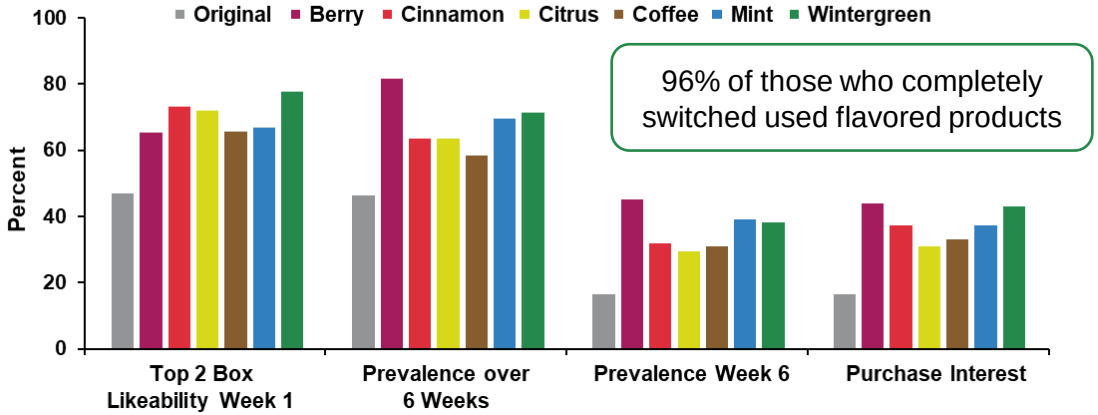


VAS=Visual Analog Scale

Consumer Preferences and Differences in Subjective Ratings Emerge in Real World Setting

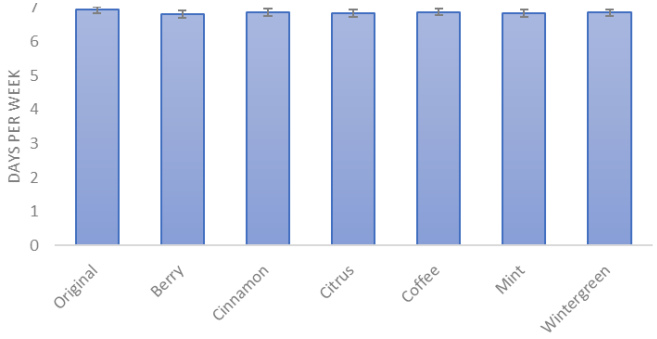
Clear flavor preference and usage under real-world conditions w/ no differences in frequency of use

Likeability, Use, and Purchase Interest (%) of on![®] Nicotine Pouches by Flavor Variety among Adult Smokers during the 6-Week Trial



96% of those who completely switched used flavored products

Mean number of days (95% CI) of on![®] nicotine pouch use by flavor variety during week 6



In-clinic data and use patterns demonstrate unlikely differences in dependence potential of various flavors but do not capture consumer preferences

Cheng, H.; Lewis, J.; Wei, L.; Becker, E., "Assessment of Actual Use Behavior for Flavored Nicotine Pouches Relative to Original Nicotine Pouches". Poster presented at the College on Problems of Drug Dependence, June 11-15, 2022. https://sciences.altria.com/-/media/Project/Altria/Sciences/presentations/2022/CPDD_2022_Cheng_Poster.pdf

Typical Tobacco AL Evaluation Should be Evaluated in the Context of Behavioral Studies to Address APPH Standard

May better inform the likelihood that current tobacco users WILL SWITCH and that new users may INITIATE and progress to regular use & DEPENDENCE

IN-CLINIC DATA +

DATA FROM ACTUAL USE AND TOPOGRAPHY STUDIES:

- Tobacco use patterns
- Subjective responses
- Future product use intentions
- Ratings of dependence* on various tobacco products (longer-term studies and postmarket surveillance)

MODELING:

- Nicotine exposure under real world conditions

DATA FROM BEHAVIORAL INTENTIONS SURVEYS:

- Intentions to try among never & former tobacco users

Should be evaluated in the context of
THE HEALTH RISK POTENTIAL OF THE PRODUCT
relative to tobacco products with known health effects
&
ACTUAL USE OF THE PRODUCT
including behavioral switching and impact on other tobacco use

*Changes in Tobacco Dependence and Association With Onset and Progression of Use by Product Type From Waves 1 to 3 of the Population Assessment of Tobacco and Health (PATH) Study - PubMed (nih.gov); Validation of the Wave 1 and Wave 2 Population Assessment of Tobacco and Health (PATH) Study Indicators of Tobacco Dependence Using Biomarkers of Nicotine Exposure Across Tobacco Products - PubMed (nih.gov)