Assessing Tobacco Product Abuse Liability in the Context of the Appropriate for the Protection of Public Health (APPH) Standard

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Abstract

For new or modified-risk tobacco product applications, the U.S. Food and Drug Administration (FDA) recommends tobacco product manufacturers provide an abuse liability assessment (ALA) of their products. In its final PMTA recordkeeping rule, FDA states that abuse liability information "…indicates the likelihood of users to become addicted to the product and face the health risks posed by product use over the long term, and provides insight into the use and adoption of the product, which is an important part of FDA's assessment of the health risks of the new tobacco product as part of its determination of the risks and benefits to the population as a whole under section 910(c)(4) of the FD&C Act." The typical approach to tobacco product ALA stemmed from the methods and framework used to evaluate pharmaceutical products, with primary outcomes derived from clinical laboratory studies that assess subjective effects (e.g., liking and satisfaction) and nicotine delivery. While this approach has successfully met FDA recommendations, recent data,, and FDA communications reveal opportunities to reevaluate the tobacco ALA framework. Controlled clinical conditions do not necessarily reflect real-world conditions or likelihood of future product use, making it difficult to infer the likelihood that product use would lead to addiction and undesirable consequences. This presentation will demonstrate why a typical tobacco ALA should be evaluated in the context of actual use behaviors including topography, tobacco use patterns, longer-term subjective responses, and intentions to continue product use to better address the appropriate for the protection of public health standards. These data, and nicotine pharmacokinetic data can serve as inputs to models that predict resultant nicotine exposure under actual use conditions. This collection of evidence can be used to infer the likelihood that the product would serve to displace more harmful tobacco use behaviors. This framework represents a more relevant and fulsome tobacco product ALA that prioritizes information that includes product preferences and real-world usage patterns, which better describes the likelihood that individuals would use the products in a way that would result in undesirable consequences relative to other tobacco products. Dependence or addiction to new tobacco products is multifaceted and influenced by several factors not easily captured in a premarket setting; FDA and others have assessment tools that could be deployed post-market to inform the dependence potential of new tobacco products relative to traditional tobacco.

Background[1]

- Abuse liability assessments (ALA) are required for new tobacco product applications and recommended for modified risk tobacco product applications.
- FDA has defined abuse liability as "…the potential of a substance to result in addiction and be used repeatedly or even sporadically resulting in undesirable consequences."
- FDA, through guidance and public engagements, has suggested that ALA should inform both the substitutability of new/modified risk tobacco products AND the likelihood of initiation and progression to regular use.
- FDA has further recommended that ALA include information on topography, patterns of use, and nicotine pharmacokinetics (PK) and pharmacodynamics (PD) (e.g., subjective effects).
- FDA suggests that 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 known abuse liability. Generally, the primary outcome measure is peak liking (Emax) as reported via a visual analog scale."
- While results of these standard abuse liability studies suffice in meeting FDA recommendations, more recent communications have indicated that the FDA feels these standard assessments may not be sufficient for some products.
  - Examination of recent data shows that the standard abuse liability study successfully distinguishes between tobacco product categories (e.g., cigarettes vs. electronic cigarettes or oral nicotine pouches; traditional moist smokeless tobacco vs. oral nicotine pouches) but does not always distinguish between tobacco products within the same category.
  - Additional information may be needed for a more fulsome abuse liability assessment of certain tobacco products.

FDA Guidance

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)

Standard tobacco product abuse liability-related information should be taken into context of actual use behaviors, longer-term subjective effects and future product use intentions as well as the health risks of the new tobacco product.

Results of standard in-clinic AL studies do not necessarily reflect real world usage patterns

❖ Individual differences in use patterns impact nicotine exposure

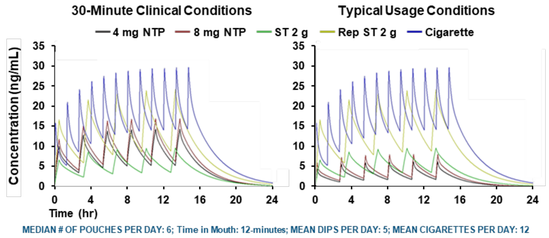
❖ Consumer product preferences impact substitutability

In-clinic conditions do not necessarily reflect nicotine exposure under actual usage conditions [1]

Modeling methods can simulate various real world usage conditions with inputs from clinical PK studies and actual use studies. Modeling scenarios can include variations in duration and amount of product use, use of multiple products at once, varying nicotine levels, and multiple usages over time.

Non-Parametric Superposition Analysis

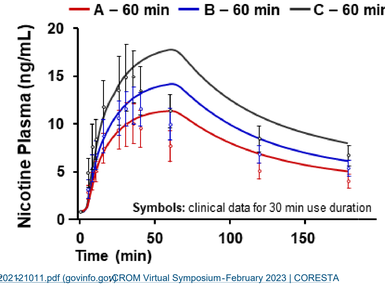
Simulated, baseline-adjusted nicotine exposure during multiple 4 and 8 mg on!® nicotine pouch product uses across a 16-hour day under controlled clinical and typical, at-home usage conditions



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

Physiologically -Based Pharmacokinetic Modeling

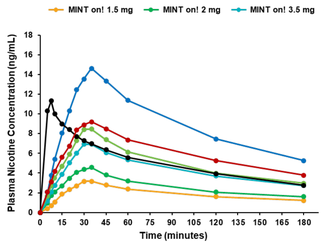
Baseline-adjusted plasma nicotine concentrations for an oral tobacco product varying in nicotine level under controlled 30-minute in-clinic usage conditions and simulated 60-minute usage conditions



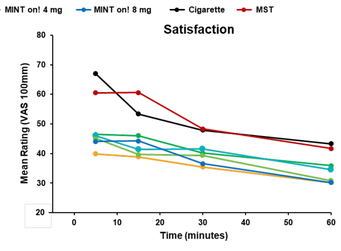
Subjective assessments do not always align with nicotine delivery [2]

Under controlled in-clinic conditions, subjective ratings of tobacco product effects do not always align to the nicotine delivery profile of the products, suggesting that other factors (e.g., sensory attributes) may influence subjective responding. Below, we see no clear distinction in subjective ratings across nicotine levels following 30-minute use of an oral nicotine pouch (ONP) product among dual users of cigarettes and moist smokeless tobacco (MST).

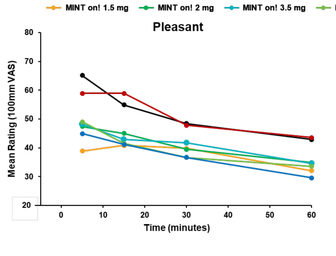
Clear Distinction in Nicotine Delivery Across Nicotine Levels



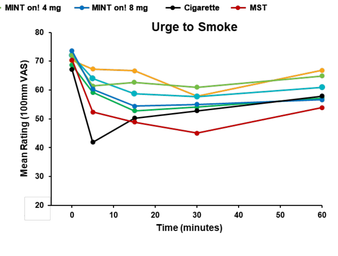
No Distinction in Satisfaction Ratings across Nicotine Levels



No Distinction in Pleasant Ratings Across Nicotine Levels



No Clear Nicotine Response on Ratings of Urge to Smoke



In-clinic nicotine delivery & subjective ratings do not always reflect real world use patterns [3]

Standard clinical study findings related to nicotine pharmacokinetics and subjective effects do not necessarily predict actual use patterns. Below, we see that, under clinical conditions, the highest nicotine level ONP garnered the least positive sentiment for *willingness to use the product again*, while the lowest nicotine level garnered the greatest positive sentiment. Under actual use conditions, however, the lowest nicotine level ONP was used by the lowest percentage of participants at the end of a 6-week trial, with all other nicotine levels being used by a similar percentage of participants. Concordantly, in-clinic data showed no differences in nicotine delivery or in subjective ratings for ONPs across a range of flavors. However, clear flavor preferences emerged under real-world conditions, with all other flavors being preferred to "original" and product flavorings contributing to the substitutability of the ONPs

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

Product (on!® Mint)	# NEUTRAL OR UNWILLING TO USE: -50 to < 0	0	# WILLING TO USE: > 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

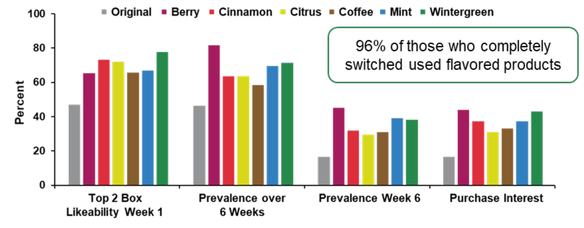
Actual Use of Product During At-home, Open-access, 6-week Use Period

% of Adult Dual Users of MST and Cigarettes Reporting Use of Each on!® Nicotine Strength — Week 6

1 mg	14.18
2 mg	28.61
3 mg	31.39
4 mg	38.99
8 mg	35.44

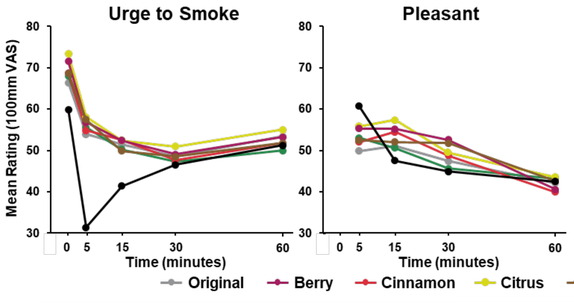
Note: The 1.5 and 1 mg and the 3.5 and 3 mg nicotine pouches were the same products – the nicotine level descriptions were updated upon further analytical testing, but we stayed true to the descriptions used in study documentation

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

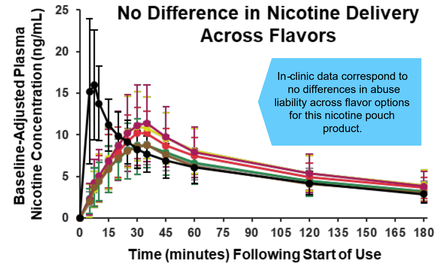


Actual use data show clear flavor preferences emerge in the natural environment with no differences in frequency o f use.

No Difference in Pleasant or Urge to Smoke Ratings Across Flavors



No Difference in Nicotine Delivery Across Flavors



In-clinic data correspond to no differences in abuse liability across flavor options for this nicotine pouch product.

Frequency of ONP use did not differ by flavor variety, and similar use durations and amount of product use were also observed.

Conclusion

- FDA suggests that an ALA should inform substitutability of new/modified risk products for more harmful forms of tobacco AND the likelihood of initiation and progression to regular use. As seen in the data examples provided here, results of the standard clinical PK-PD study does not necessarily predict product preferences, use patterns, or nicotine exposure under naturalistic conditions,
- Importantly, in-clinic conditions do not reflect real world or actual usage conditions. While clinical PK-PD study continues to provide valuable information regarding nicotine uptake and subjective effects under controlled conditions, these data may not suffice for a full ALA.
- A more holistic ALA would include data from standard in-clinic studies and may be further informed by actual use (including impact on other tobacco use behaviors), product use topography, subjective ratings under real world or longer-term usage conditions, and nicotine PK modeling that estimates nicotine exposure under naturalistic conditions. Finally, a fulsome ALA should consider the relative health risks of the new or modified risk product.
- To better inform the likelihood of tobacco product use, information regarding intentions to use among nonusers or initiation rates for similar tobacco products may be taken into consideration alongside the ALA.

1. Sources: 202121011.pdf (govinfo.gov); CROM Virtual Symposium-February 2023 | CORESTA

2. Sources: Vansickel, Nguyen, Edmiston, Sarkar (2021). Pharmacokinetic modeling and simulation of single and multiple uses of an oral tobaccoderived nicotine product compared to moist smokeless tobacco products and combustible cigarettes under actual use conditions. Poster presented at the 27 Annual Society for Research on Nicotine and Tobacco Meeting; comprehensive physiologically based pharmacokinetic (PBPK) model for nicotine in humans from using nicotine-containing products with different routes of exposure - PMC (nih.gov)

3. Source: 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)

4. Sources: 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); Characterization of Ad Libitum Use Behavior of On! Nicotine Pouch… - Ingenta Connect; Nicotine pharmacokinetics and subjective response among adult smokers using different flavors of on!® nicotine pouches compared to combustible cigarettes | Psychopharmacology (springer.com)

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