

End-to-End Review of an ENDS Product PMTA Science Package: VUSE Case Study



Jenna Guynn, PhD, DABT | Senior Director – Scientific & Regulatory Affairs

Contents Disclaimer



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Disclosures

- The following studies were sponsored by RAI Services Company
- Jenna Guynn is a full-time employee of RAI Services Company

VUSE Alto Marketing Granted Orders Received on July 18, 2024



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Based on my review of the subject PMTAs and the available evidence, I find that permitting the marketing of the new products... is **appropriate for the protection of the public health.**

FDA (2024). PMTA Technical Project Lead Review, PM0000973.PD1, PD2, PD3, PD6, PD7, PD10, PD11; emphasis added.

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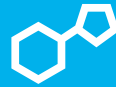


VUSE Alto PMTAs Included a Comprehensive, Multi-Disciplinary Science Package



Design & Manufacturing

- Design, ingredients, packaging
- Manufacturing processes and controls, supplier qualification
- Draw resistance
- Airflow rate



Properties

- Aerosol HPHCs
- Chemical & microbial stability
- Simulated & aerosol leachables
- Thermal profiling
- Particle size



Preclinical Studies

- Mutagenicity
- Genotoxicity
- Cytotoxicity
- Oxidative Stress



Individual Health

- Nicotine pharmacokinetics
- Abuse liability
- Topography



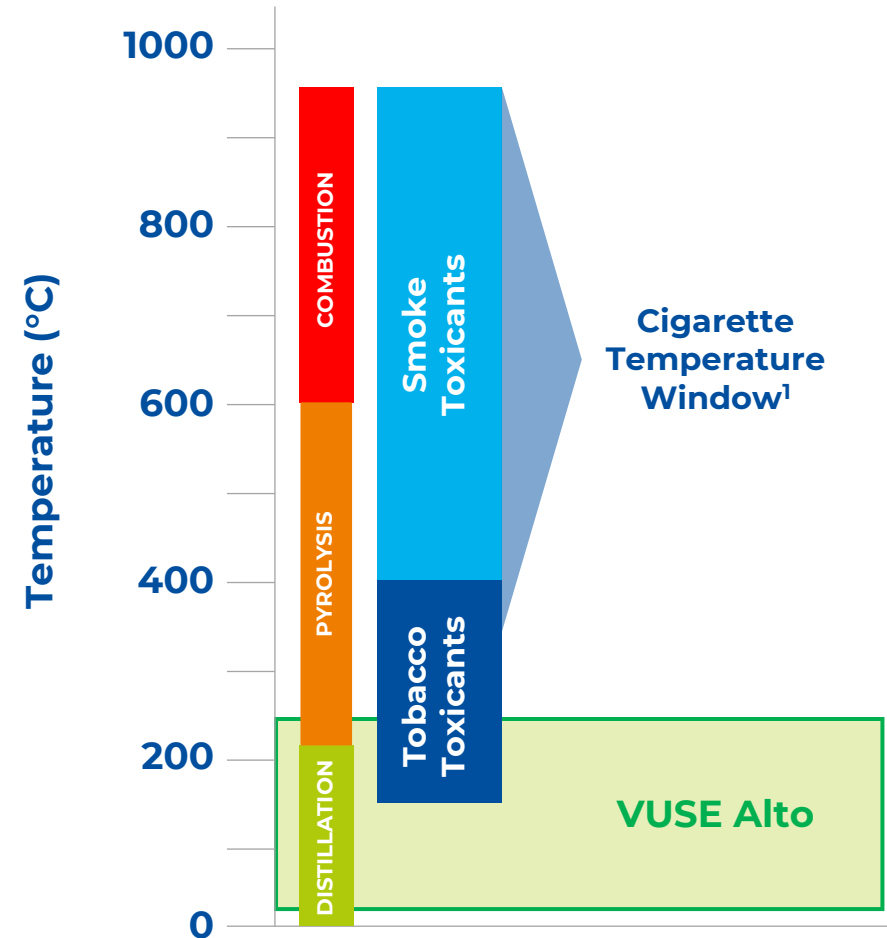
Population Health

- Actual use
- Perceptions and intentions
- Population modeling

VUSE Alto Operates at Temperatures Below Those Known to Occur in Combustible Cigarettes

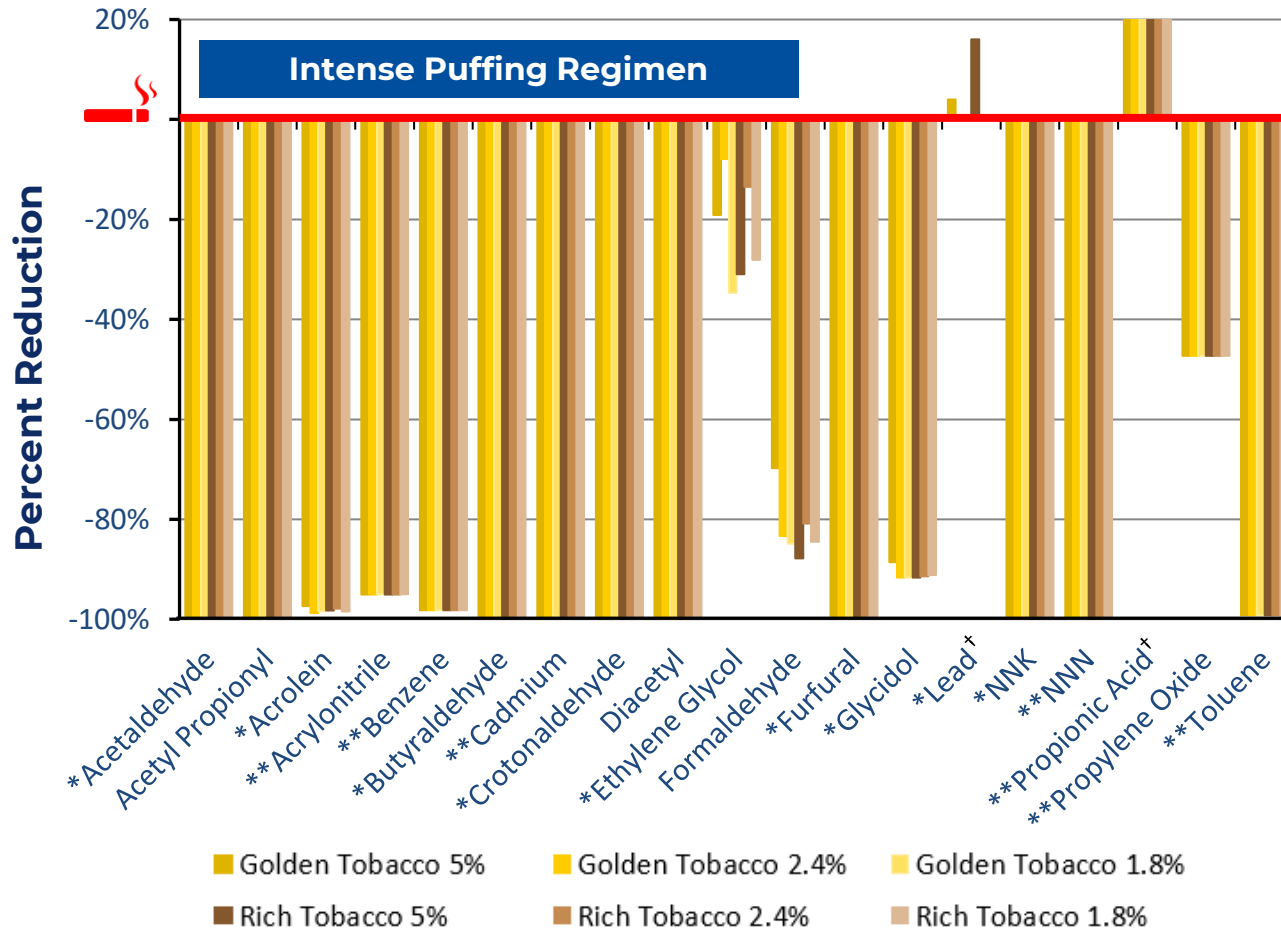
Thermal Profiling

- Thermocouples placed at target locations in/on the:
 - Cartridge
 - Power unit
 - Aerosol stream
- Temperatures measured under non-intense and intense puffing regimens for the full life cycle of the cartridge
 - 5 replicates/puffing regimen



¹Baker, R. R. (2006). "Smoke generation inside a burning cigarette: Modifying combustion to develop cigarettes that may be less hazardous to health." *Progress in Energy and Combustion Science* 32(4): 373-385.

VUSE Alto Aerosols Contain Fewer HPHCs Than Combustible Cigarettes



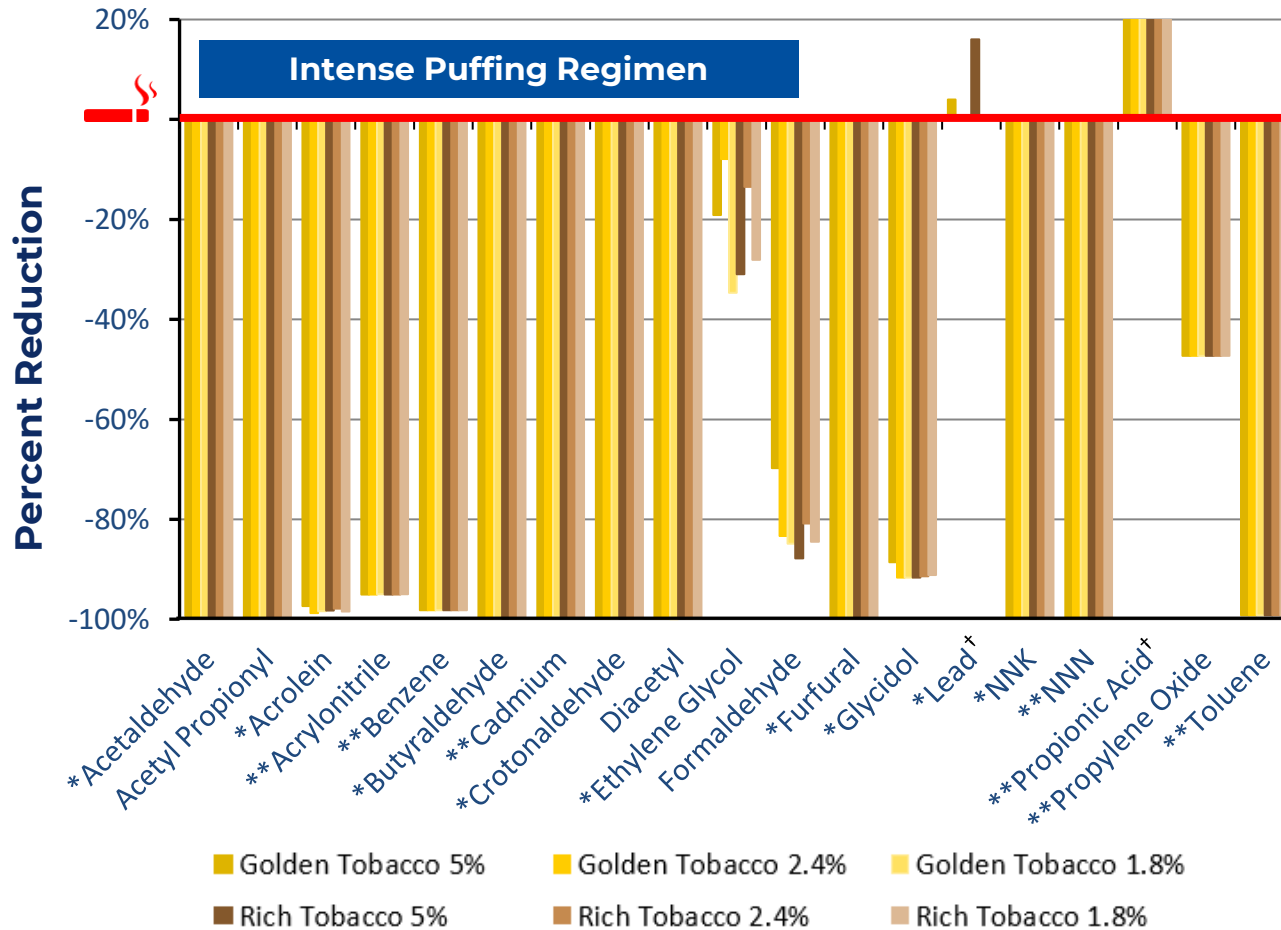
VUSE Alto Aerosol Generation Puffing Regimens		
Variable	Non-Intense	Intense
Volume (mL)	55	80
Duration (sec)	3	5
Inter-puff Interval (sec)	30	15
Cartridge life cycle (puffs)	270	130

Other constituents analyzed:
Benzyl acetate, Chromium, Diethylene Glycol, Ethyl acetate, Ethyl acetoacetate, Ethylene Glycol, Glycerin, Isoamyl acetate, Isobutyl acetate, Menthol, Methyl acetate, N-butanol, Nickel, Propylene Glycol
 (< LOQ for all VUSE Alto replicates)

***Some VUSE replicates were < LOQ **All VUSE replicates were < LOQ**

[†] Note: The LOQs for lead and propionic are numerically equivalent to or higher than, respectively, the reported mean values in combustible cigarette smoke. Therefore, the levels for lead and constituent increase noted for propionic acid versus combustible cigarette smoke are likely overestimated.

VUSE Alto Aerosols Contain Fewer HPHCs Than Combustible Cigarettes



...the new products' aerosols have **fewer HPHCs than CC smoke** and many of the HPHCs present in the aerosols have **comparatively lower potencies** (*i.e.*, lower magnitude or severity of toxicological effect at a given dose or exposure level) than those present in CC smoke.

FDA (2024). PMTA Technical Project Lead Review, PM0000973.PD1, PD2, PD3, PD6, PD7, PD10, PD11; emphasis added.



Other constituents analyzed:

Benzyl acetate, Chromium, Diethylene Glycol, **Ethyl acetate**, **Ethyl acetoacetate**, Ethylene Glycol, Glycerin, **Isoamyl acetate**, **Isobutyl acetate**, Menthol, **Methyl acetate**, **N-butanol**, Nickel, Propylene Glycol

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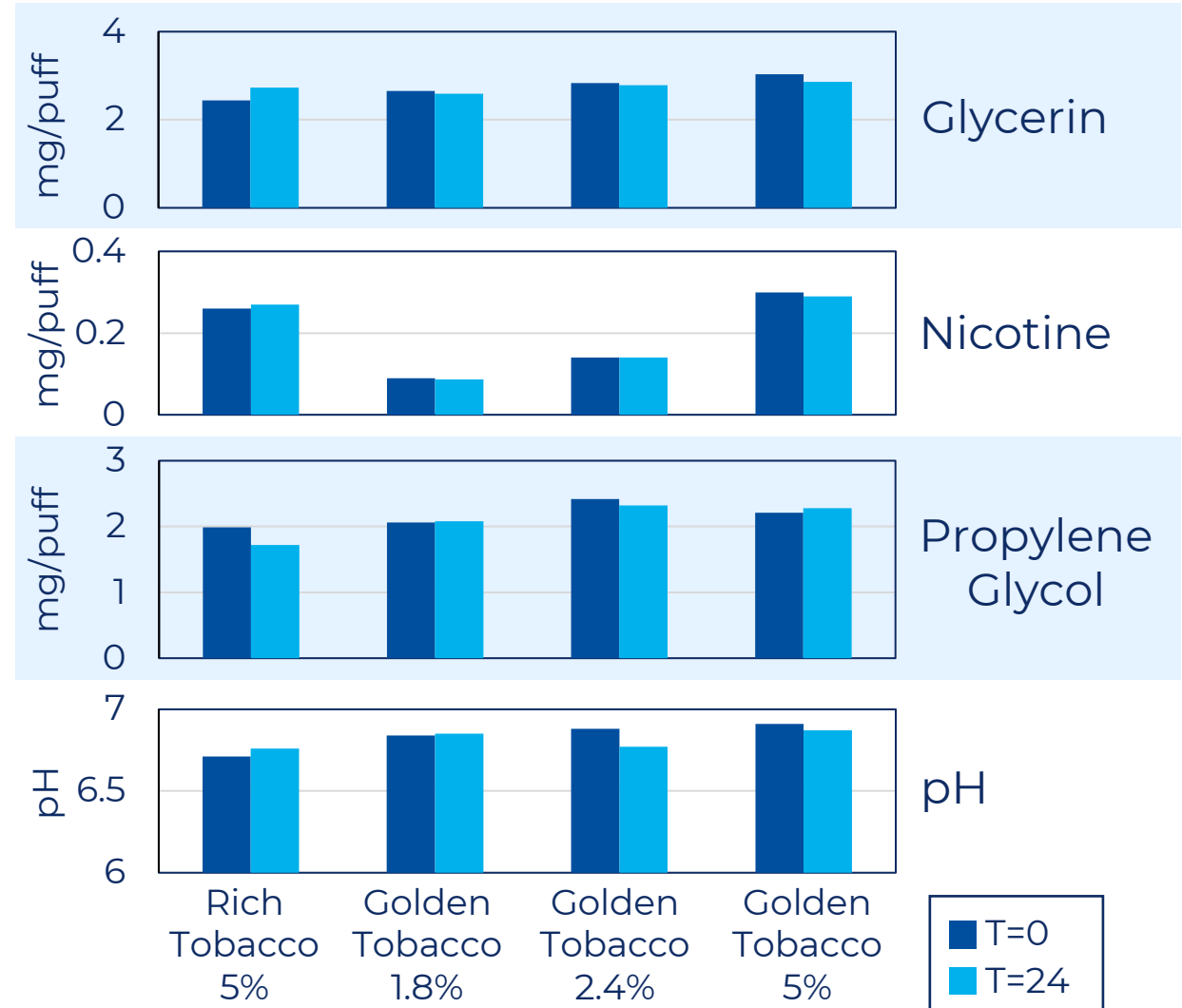
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Chemical Stability Data Support the Intended Shelf Life of VUSE Alto Products

Chemical Stability

- Evaluated over 24 months
- Three manufacturing batches of each sample
- Non-intense and intense puffing regimens
- Long Term storage conditions (25°C/60%RH)
- Aerosol evaluated for:
 - HPHCs
 - pH



Microbial Stability Data Support the Intended Shelf Life of VUSE Alto Products

Microbial Stability

- Evaluated over 24 months
- Three manufacturing batches of each product
 - Golden Tobacco 5%, 2.4%, and 1.8%
 - Rich Tobacco 5%
- Long Term storage conditions (25°C/60%RH)
- E-liquid evaluated for:
 - Total aerobic microbial counts (TAMC)
 - Total yeast and mold counts (TYMC)
 - TSNAs
 - Water Activity

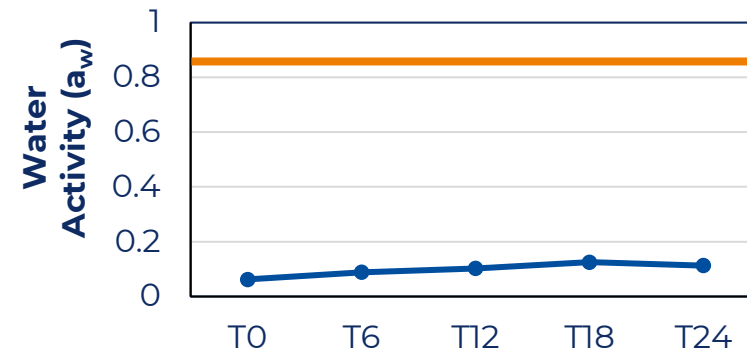
TAMC

TYMC

TSNAs

Below the limit of quantitation for all VUSE Alto e-liquids tested

Water Activity



Water activity threshold for microbial growth¹

¹ FDA. (1984). Inspection Technical Guide No. 39. Water Activity (aw) in Foods.



Leachables Studies of VUSE Alto Inform Shelf Life and Risk Characterization

Simulated Leachables

Simulation study with e-liquids

- Evaluated VUSE Alto cartridge components with potential to contact the e-liquid, aerosol, or heated inlet air
- Components were submerged in e-liquids for 33 days at 60 °C to simulate 12-month storage at 25 °C

Aerosol Leachables

Actual Leachables in aerosol

- VUSE Alto cartridges were stored at Long Term conditions (25°C & 60% relative humidity) for up to 24 months
- Aerosol evaluated via targeted leachables and untargeted scans

Elements or Compounds Present
>1.5 µg/day*

13

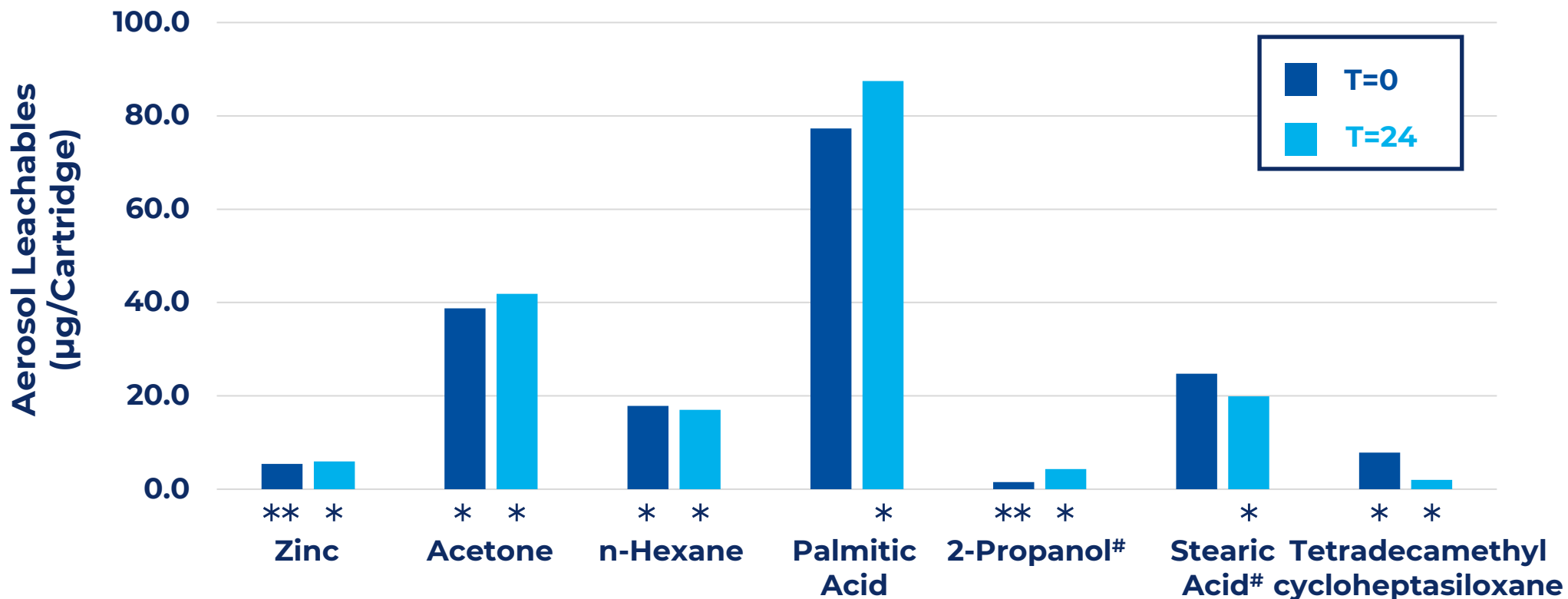
Simulated
Leachables

7

Aerosol
Leachables

*Based on estimated daily product use of 1 cartridge/day

Leachables Studies of VUSE Alto Inform Shelf Life and Risk Characterization



*Some VUSE replicates were < LOQ or <1.5 µg/cartridge

**All VUSE replicates were < LOQ or <1.5 µg/cartridge

#Estimated value derived from the untargeted scans

VUSE Alto Aerosols are Non-Genotoxic, Non-Mutagenic, Non-Cytotoxic and Induce Lower Levels of Oxidative Stress

	Combined TPM + GVP			Whole Aerosol/Smoke		
	Ames Mutagenicity ¹	ivMN Genotoxicity ¹	NRU Cytotoxicity ¹	NRU Cytotoxicity ²	EpiAirway Cytotoxicity ²	EpiAirway Oxidative Stress ²
Golden Tobacco 5%	Negative	Negative	Negative	Negative	Negative	↓
Rich Tobacco 5%	Negative	Negative	Negative	Negative	Negative	↓
Golden Tobacco 2.4%	Negative	Negative	Negative	Negative	Negative	↓
Golden Tobacco 1.8%	--	--	--	Negative	Negative	No Induction*
ENDS Comparator	Negative	Negative	Negative	Negative	Negative	No Induction*
Combustible Cigarette Comparator	Mutagenic	Genotoxic	Cytotoxic	Cytotoxic	Cytotoxic	↑

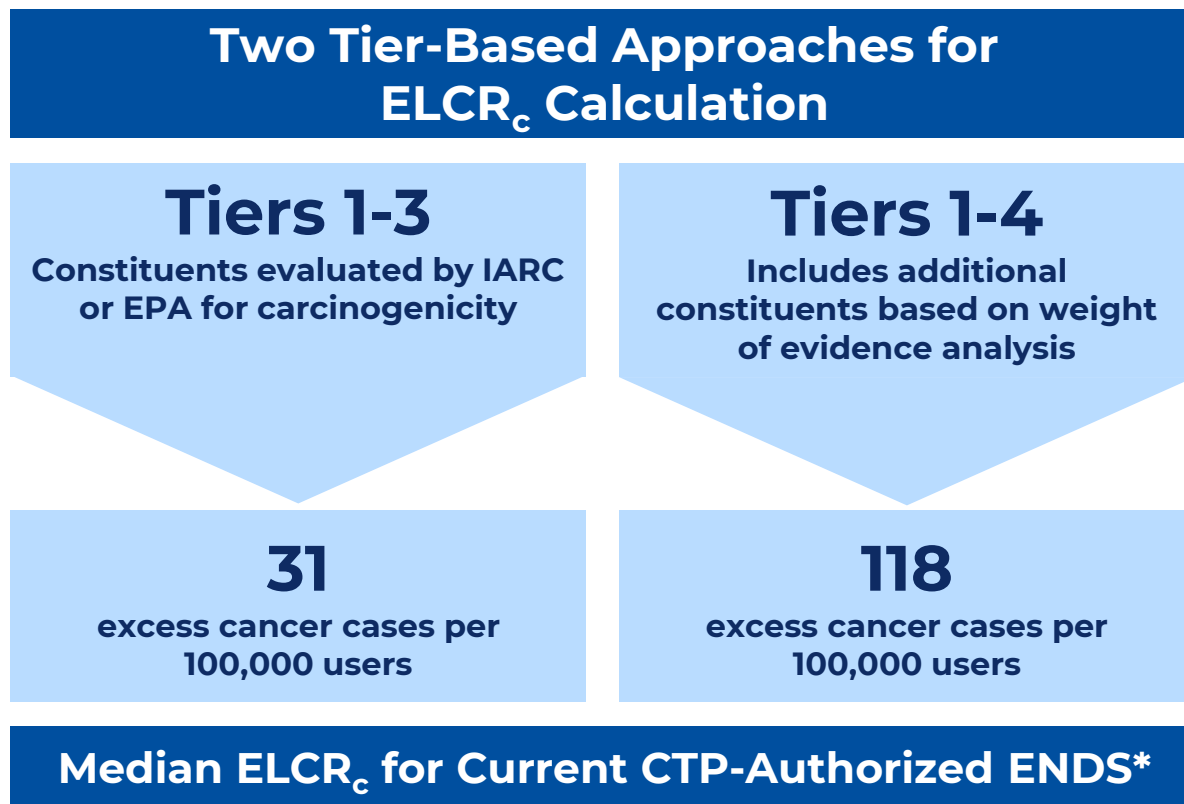
*Induction of oxidative stress threshold is 2-fold increase in Nrf2 reporter gene activity
 TPM = total particulate matter; GVP = gas vapor phase

¹ Keyser et al. (2024) *Toxics*, 12(2), 129.

² Leverette et al. *Food Chem Toxicol*, submitted



FDA's Toxicology Review Notes Limitations With Genotoxicity Assay Results and Calculates Cumulative Excess Lifetime Cancer Risk (ELCR_c)



*As of February 2024

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When the risk assessment includes Tier 1 – 4 constituents, the ELCR_c for the new [VUSE Alto] products fall between 1 – 10% of the 1R6F CC ELCR_c indicating **lower cancer risk** relative to CC.

FDA (2024). PMTA Technical Project Lead Review, PM0000973.PD1, PD2, PD3, PD6, PD7, PD10, PD11; emphasis added.

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Product Use and Behavior (PUB) Instrument Captures Puffing Data in a Real-World, Ambulatory Setting

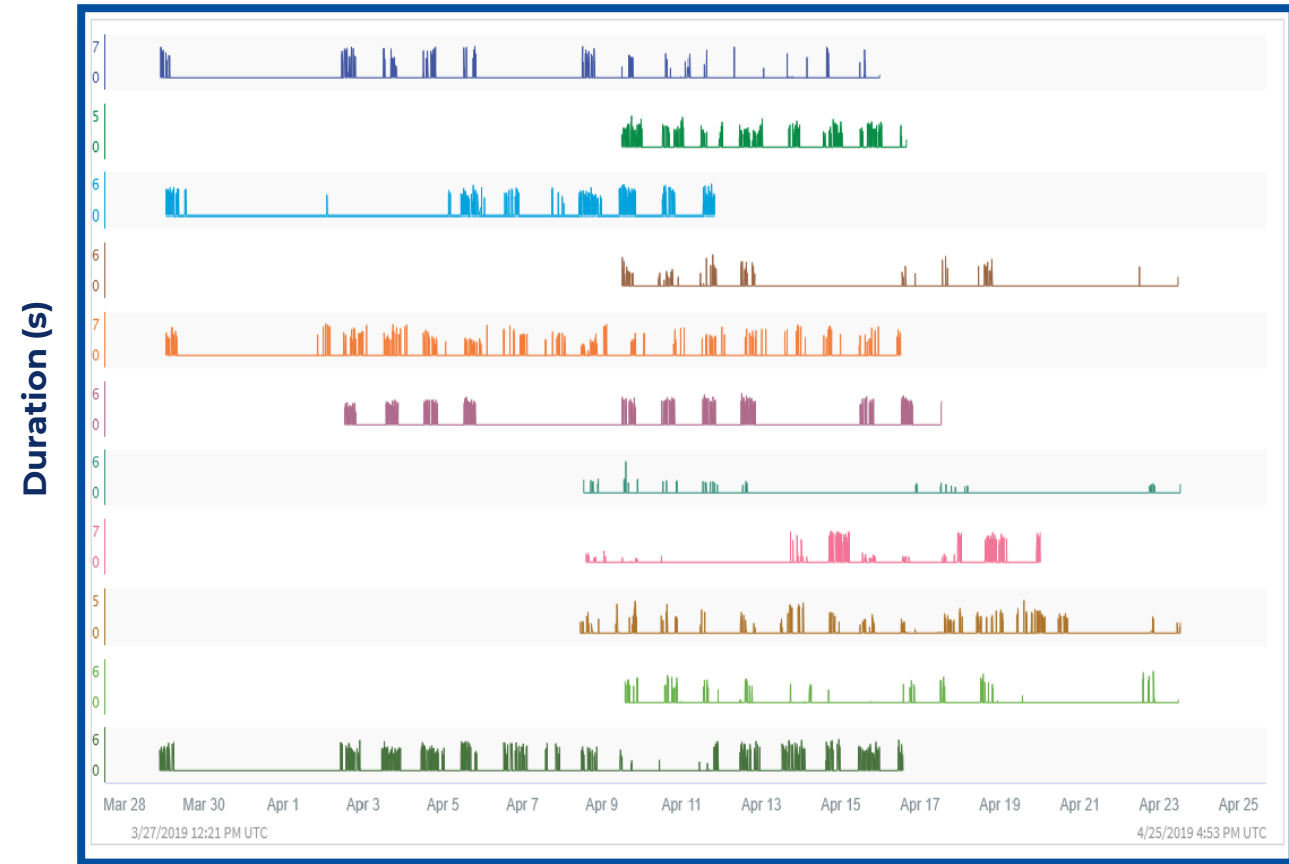
PUB Instrument



- Puff duration (seconds)
- Number of puffs (count)
- Sessions of use (count)
- Inter puff interval (seconds)
- Angle of Use (XYZ planes)

Study Design

- Subjects were randomized to 2.4% or 5% nicotine concentration products, then assigned to 1 of 4 flavor variants* based on usual brand ENDS preference
- Following a 1-week *ad libitum* acclimatization period, data was collected via PUB during a 2-week ambulatory evaluation period



*Study included additional VUSE Alto products

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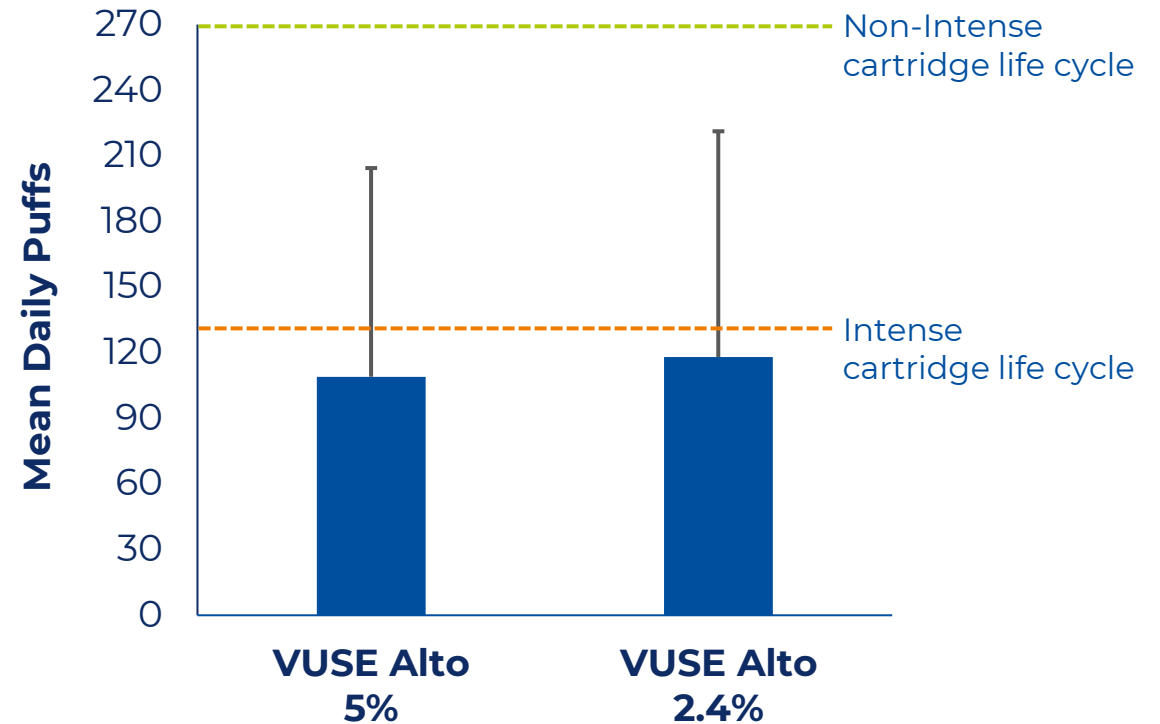
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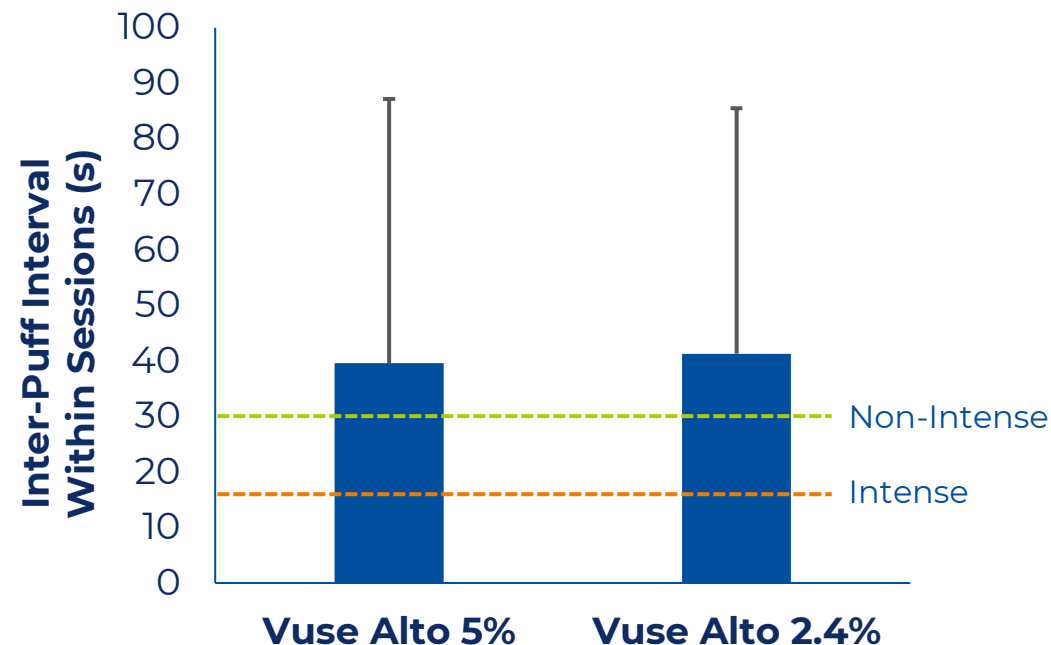
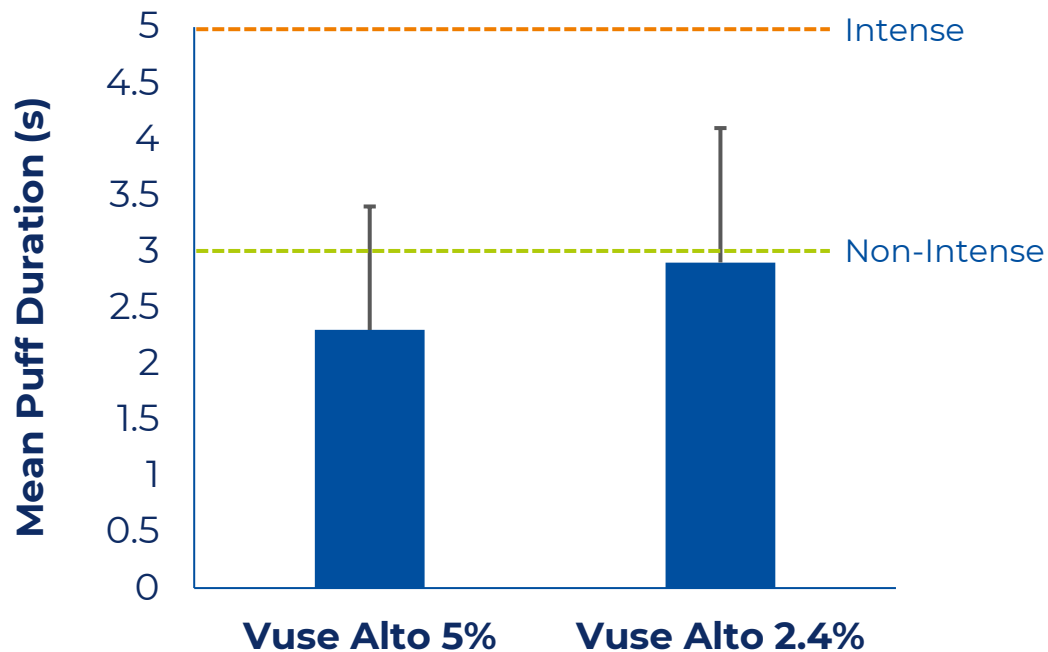
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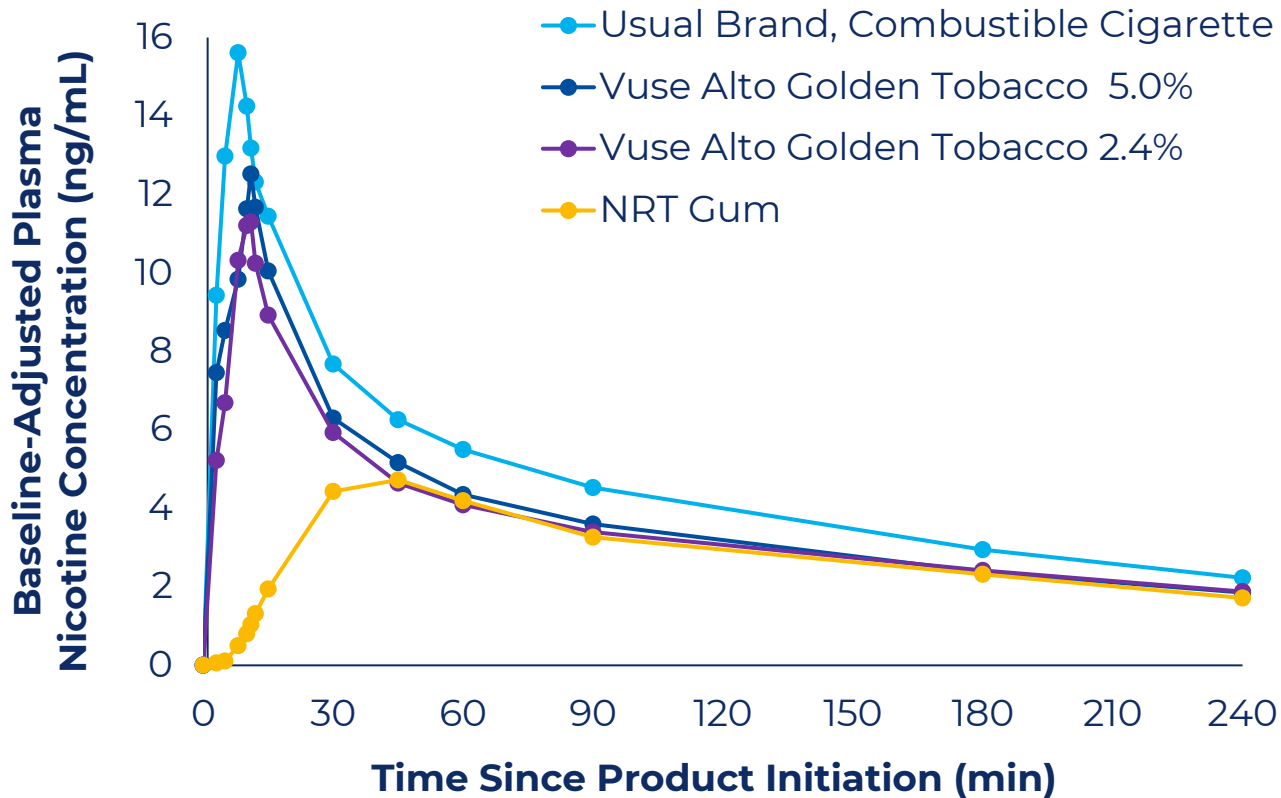


VUSE Alto Topography Study Provides Context for Machine Generated Aerosol Data



Puff parameters align more closely to machine generated non-intense puffing regimen

Abuse Liability of VUSE Alto Likely Falls Between Combustible Cigarettes and NRT



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The nicotine levels that adults who use the new products might reach, and corresponding abuse liability, indicate that the addiction risk of the new products is no higher than other currently available tobacco products.

FDA (2024). PMTA Technical Project Lead Review, PM0000973.PD1, PD2, PD3, PD6, PD7, PD10, PD11.

”

NRT = Nicotine replacement therapy



Tobacco Use History Among Adult Current Established VUSE Users

National Tobacco Behavior Monitor (Nov. 2019 – Apr. 2020)

Tobacco Product Use	Current Established Users of VUSE Alto (n = 38)
Any Tobacco Product Use	
No Use ¹	2.6%
Use	97.4%
Cigarettes	
No Use ¹	8.4%
Use ²	91.6%
<i>Current established</i>	64.5%
<i>Former established</i>	27.1%

¹"No use" defined as no use in the past 30 days, never reached 100 lifetime use threshold, and never using for at least 10 days in any 30-day period.

²No users reported being current or former cigarette experimenters

PATH Study Wave 7 (2022-2023) Confirmatory Analysis

Among current VUSE users:

- Nearly all (96.4%) have ever smoked a cigarette
- More than half (55.0%) are former established smokers³
 - Most (63.1%) indicated they quit within the last 12 months⁴
- 3.6% have never been a cigarette smoker

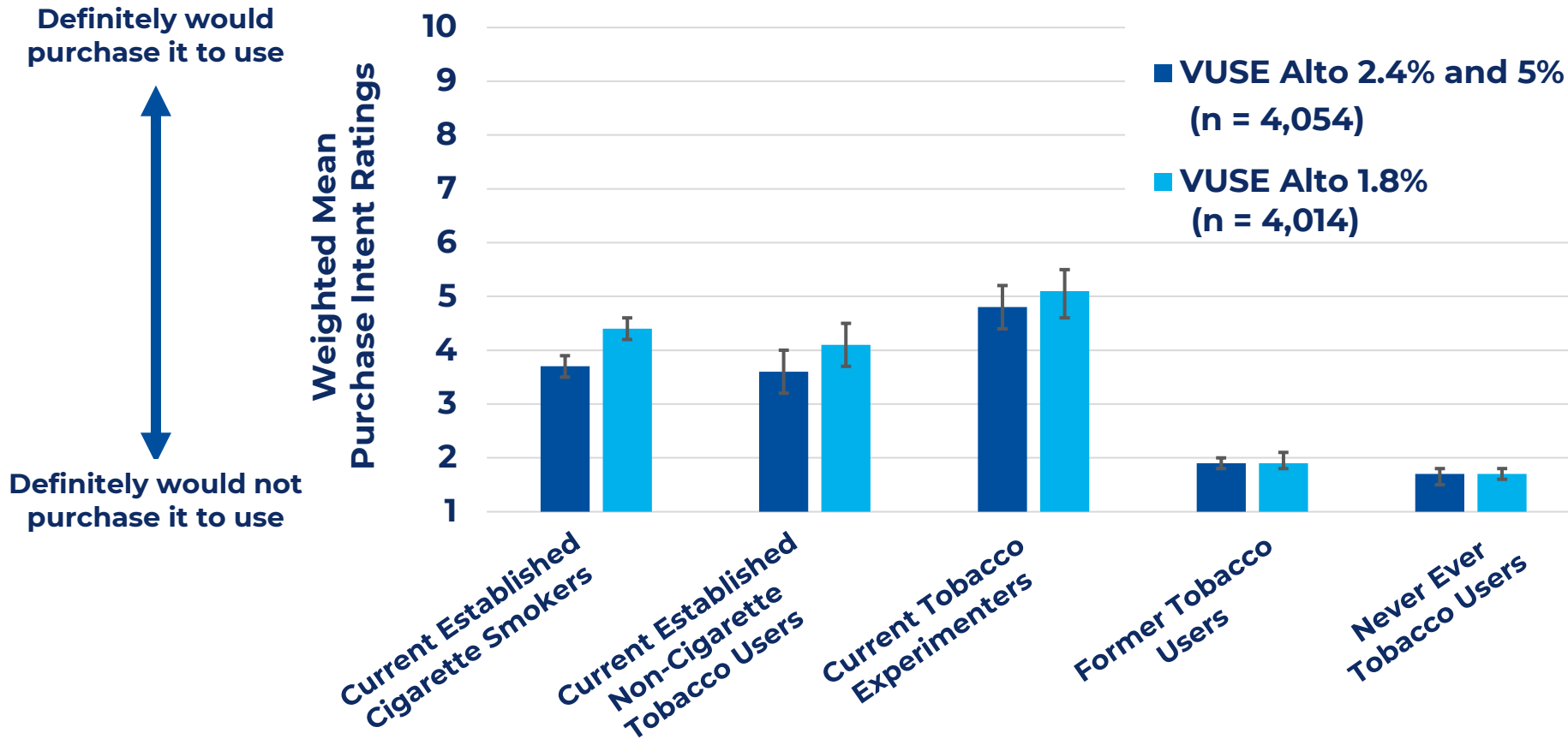
FDA (2024). PMTA Technical Project Lead Review, PM0000973.PD1, PD2, PD3, PD6, PD7, PD10, PD11.

³Having smoked >100 cigarettes in their lifetime and have not smoked them within 12 months or are not currently smoking them at all

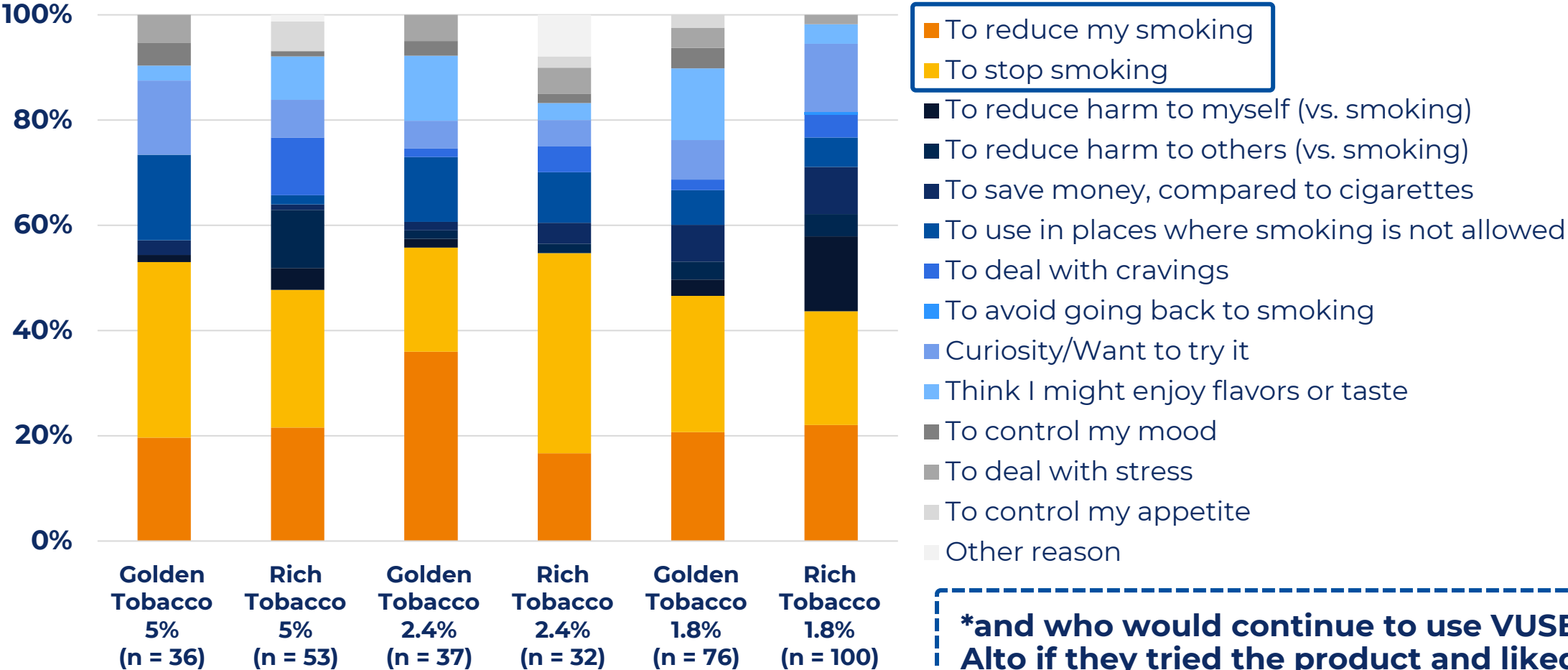
⁴Among those who provided the length of time since their last smoked cigarette



VUSE Alto Purchase Intentions are Higher in Tobacco Product User Groups Compared to Non-User Groups

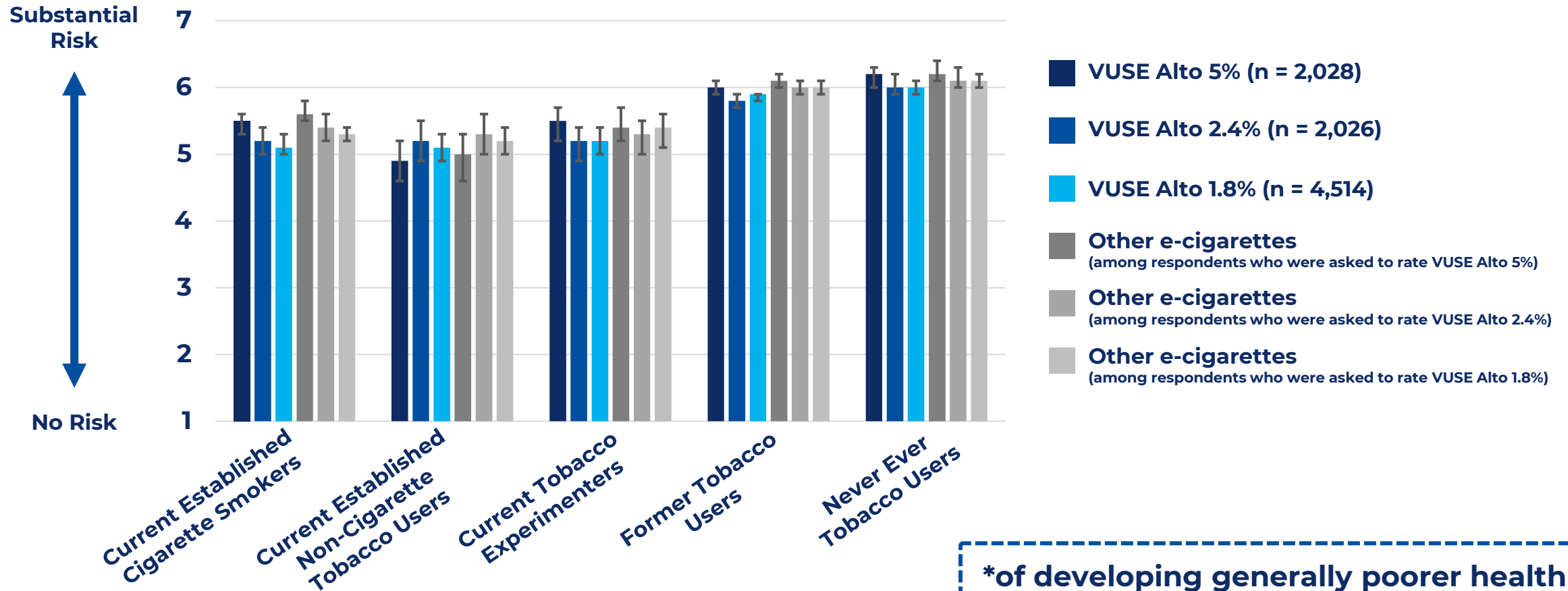


Main Reasons for Using Among Current Established Cigarette Smokers Expressing Any Interest in VUSE Alto*



***and who would continue to use VUSE Alto if they tried the product and liked it**

VUSE Alto Perceived Risk* is Higher Amongst Unintended Users and Similar to Other ENDS Products





VUSE Alto Modeling Projects Overall Population Health Benefit

Dynamic Population Modeler, DPM(+1)

Validated model provides high confidence that a marketing authorization would benefit the population as a whole.

- Integrated the effects of both potentially beneficial and harmful tobacco use patterns
- Included relative risk estimates of 0.05 and 0.10, compared to cigarettes

Projected population health benefit of VUSE Alto:

~265,000 – 405,000

additional survivors over a 60-year period*



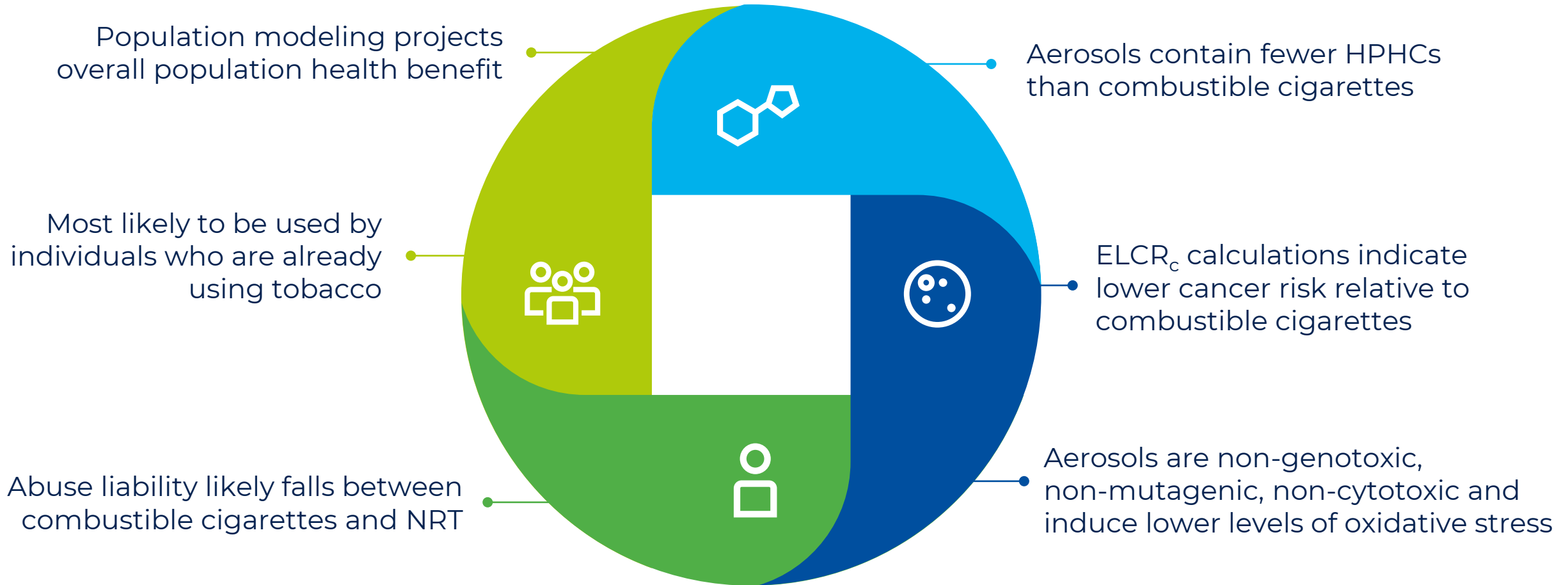
...these population health impact models provide **evidence to support an APPH finding** for the new products.

FDA (2024). *PMTA Technical Project Lead Review, PM0000973.PD1, PD2, PD3, PD6, PD7, PD10, PD11*; emphasis added.



***based on ratios of excess relative risk up to 0.10 and conservative probabilities of potentially harmful tobacco use transitions**

VUSE Alto PMTAs Contained Sufficient Evidence Demonstrating that Marketing of the Products would be APPH



Tobacco Harm Reduction is *A Better Way to A Better Tomorrow™*

Our science & technology is bringing potentially reduced risk alternatives to the almost 30 million adult smokers. Knowledge and choice drive change.

REYNOLDS 