



The Application of the Horwitz-Thompson Equation for Establishing Acceptance Criteria for Method Validation

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Background & Objective



2025 Method Validation Guidance introduced a new approach: Use **Total Error Probability** (TEP) as a metric for method acceptability, with the Horwitz–Thompson (HT) equation suggested as a tool to set concentration-dependent acceptance criteria performance

Validation and Verification of Analytical Testing Methods Used for Tobacco Products, FDA CTP, January 2025, docket FDA-2021-D-0756

Objective



Demonstrate how Horwitz-Thompson predicted variability can be translated into TEP acceptance criteria

Discuss how TEP acceptance criteria may perform in practice

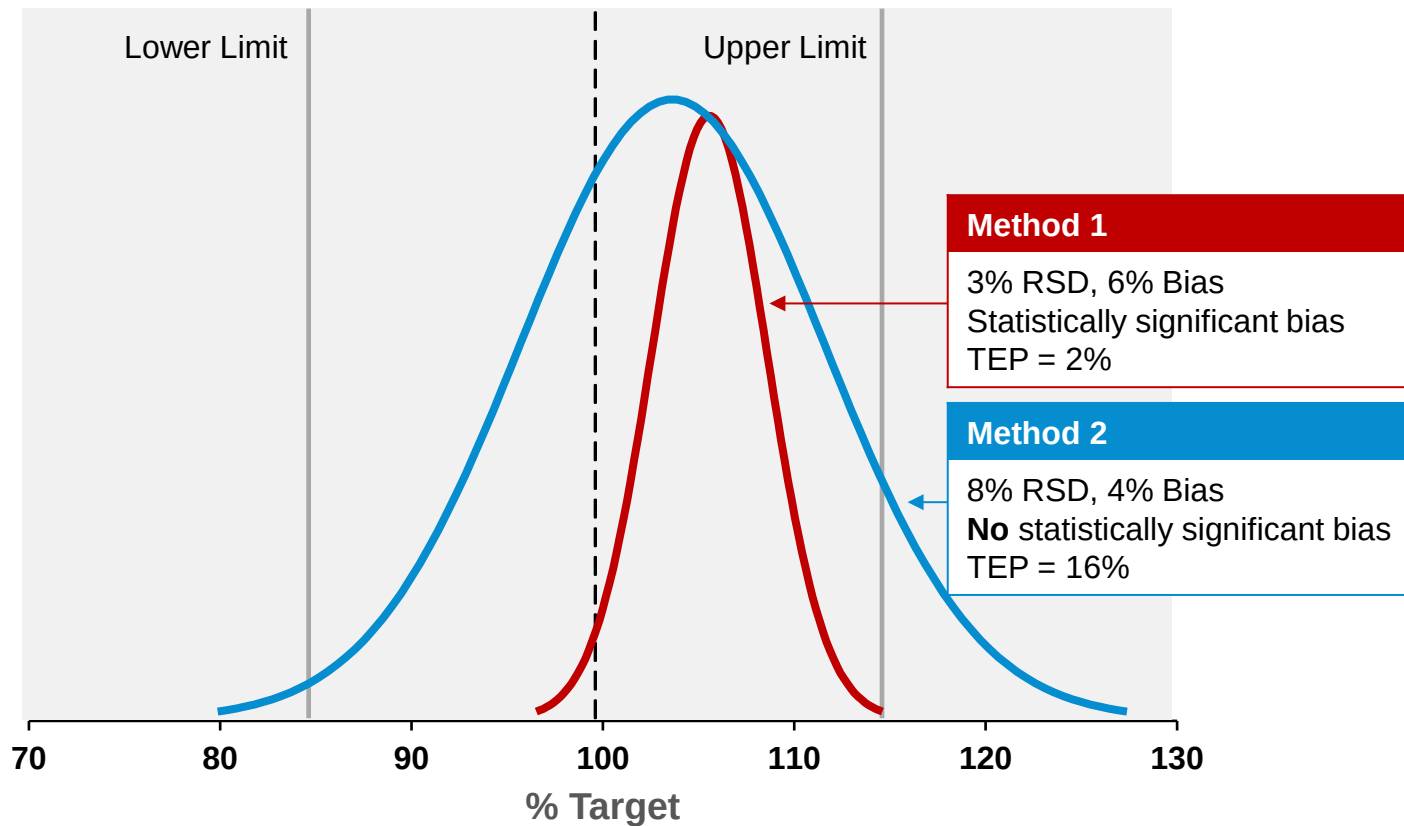
Compare HT predictions with reproducibility data from smoke-free product analytical methods

Discuss circumstances where HT-derived criteria may not reflect observed method performance



TEP Concept

Reframes validation as a prediction problem which combines accuracy and precision to assess whether future measurements are likely to fall within required acceptance limits



FDA's guidance generally **expects $\geq 95\%$ probability** that a future measurement will land inside the acceptance limits (**$\leq 5\%$ total error probability**)

TEP focuses on future measurement performance rather than statistical significance of individual parameters

Horwitz-Thompson: A Benchmark for Expected Analytical Variability



Concept

The Horwitz-Thompson (HT) equation estimates the reproducibility standard deviation expected for an analyte at a given concentration.

Expected variability increases as concentration decreases



Why this matters for TEP

- Provides a concentration-dependent variability benchmark
- Can be translated into prediction intervals
- Helps develop limits for TEP calculation

HT Equations (Concentration)

LOW

$$\sigma_R = 0.22C$$

$$C < 120 \frac{ng}{g}$$

INTERMEDIATE

$$\sigma_R = 0.02C^{0.85}$$

$$120 \frac{ng}{g} \leq C < 13.8\%$$

HIGH

$$\sigma_R = 0.01\sqrt{C}$$

$$13.8\% \leq C$$

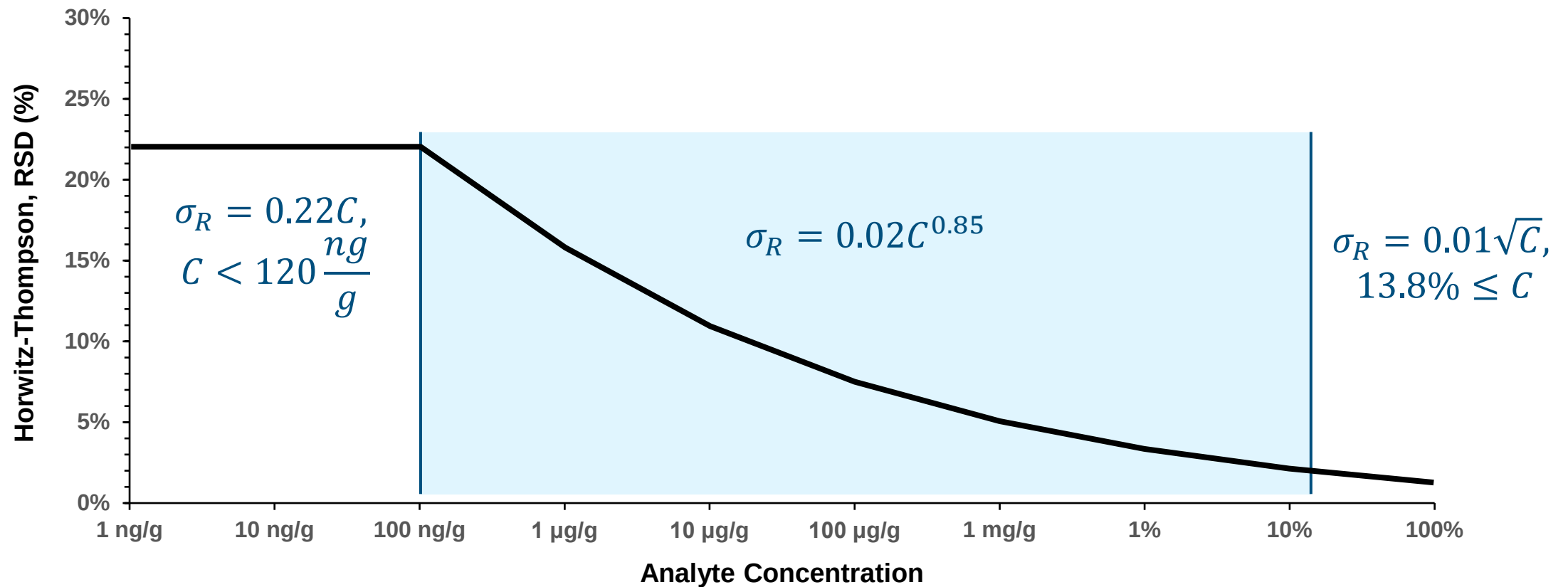
HT is not an acceptance criterion; it is a benchmark used to estimate expected method variability

Where C is the mass/mass concentration, and σ_R is the reproducibility standard deviation.



Horwitz-Thompson Predicted Reproducibility

HT implies that acceptable variability should become progressively larger as analyte concentration decreases



Proposed Approach: Translating HT Variability Into TEP Acceptance Limits

Concentration-specific HT precision estimates can be translated into TEP acceptance limits

1 Target level

Example constituent:
1 mg/g = 0.1%
Mass fraction:
C = 0.001

2 HT prediction

Predicted reproducibility:
 $RSD_R = 2C^{-0.15}$
At C = 0.001:
 $RSD_R = \sim 5.6\%$

3 Proposed: 95% prediction interval

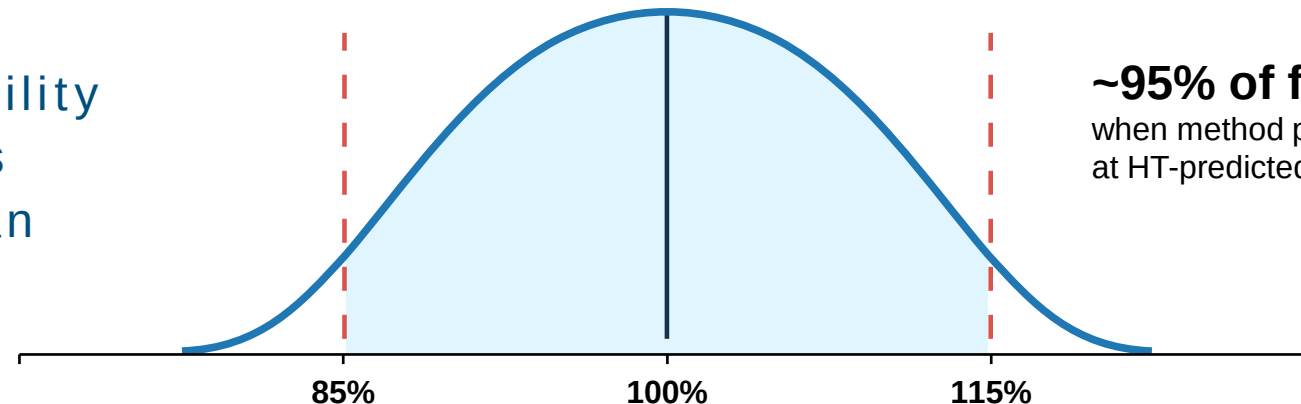
Use the predicted RSD as the expected method variability.
Calculate the interval expected to contain future results.

$$PI = \bar{x} \pm t_{n-1} RSD_R \sqrt{1 + 1/n}$$

4 Candidate limits

95% prediction interval:
~100% +/- 15%
Preliminary TEP criterion:
85% to 115%

HT supplies the variability assumption; TEP turns that assumption into an acceptance range



~95% of future results
when method performs
at HT-predicted variability



Why a Prediction Interval for HT-Derived TEP Limits?

Limits = $100\% \pm k \times \text{RSD_HT}$. TEP evaluated for a method performing exactly at Horwitz (observed RSD = RSD_HT, no bias), $n = 7$

k (multiplier on HT-RSD)	TEP	Meets ≤ 0.05 ?	Pass rate
1.00 HT-RSD as the limit	0.386	No	0.5%
1.50	0.210	No	5.3%
2.00	0.111	No	21.0%
2.62	0.050	Yes (exactly)	52.9%
3.00	0.031	Yes	71.9%
3.50	0.017	Yes	88.6%
4.00	0.010	Yes	96.5%

Pass rate = probability a single study yields TEP ≤ 0.05 when the true SD = HT-SD (simulated, 10^6 draws).

Multiplier is set by n – not chosen

$$k * t_{1-\alpha/2, n-1} * \sqrt{1 + 1/n}, \alpha = 0.05$$

$N = 5 \rightarrow 3.04$ $n=6 \rightarrow 2.78$ $n=7 \rightarrow 2.62$

Each lands TEP at exactly 0.05

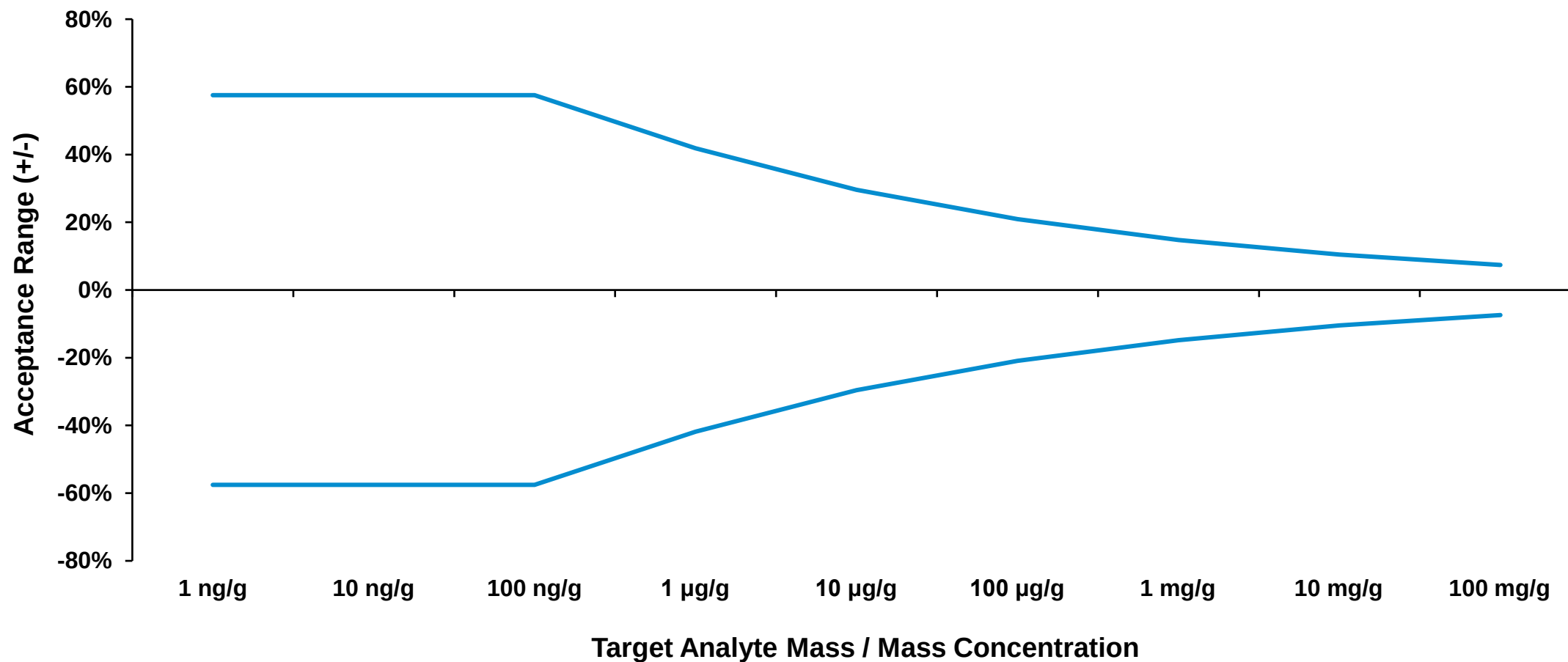
- For a method performing exactly at the HT expectation, using HT RSDs directly as TEP limits yields TEP = 0.39 – nearly 8x the 0.05 criterion
- Passing it would require an observed RSD 2.6 x lower than HT
- The 95% prediction interval multiplier (2.62 at $n = 7$) is the smallest expansion at which a HT-conforming method meets TEP = 0.05 and is a conservative floor

The expansion factor is derived from the TEP equation –

RSD appears in the denominator as $\text{RSD} * \sqrt{1 + 1/n}$, so limits set at $\pm 1 \times \text{RSD}$ are inconsistent with the criterion they are tested against



HT Predicts Progressively Wider Limits at Low Concentrations



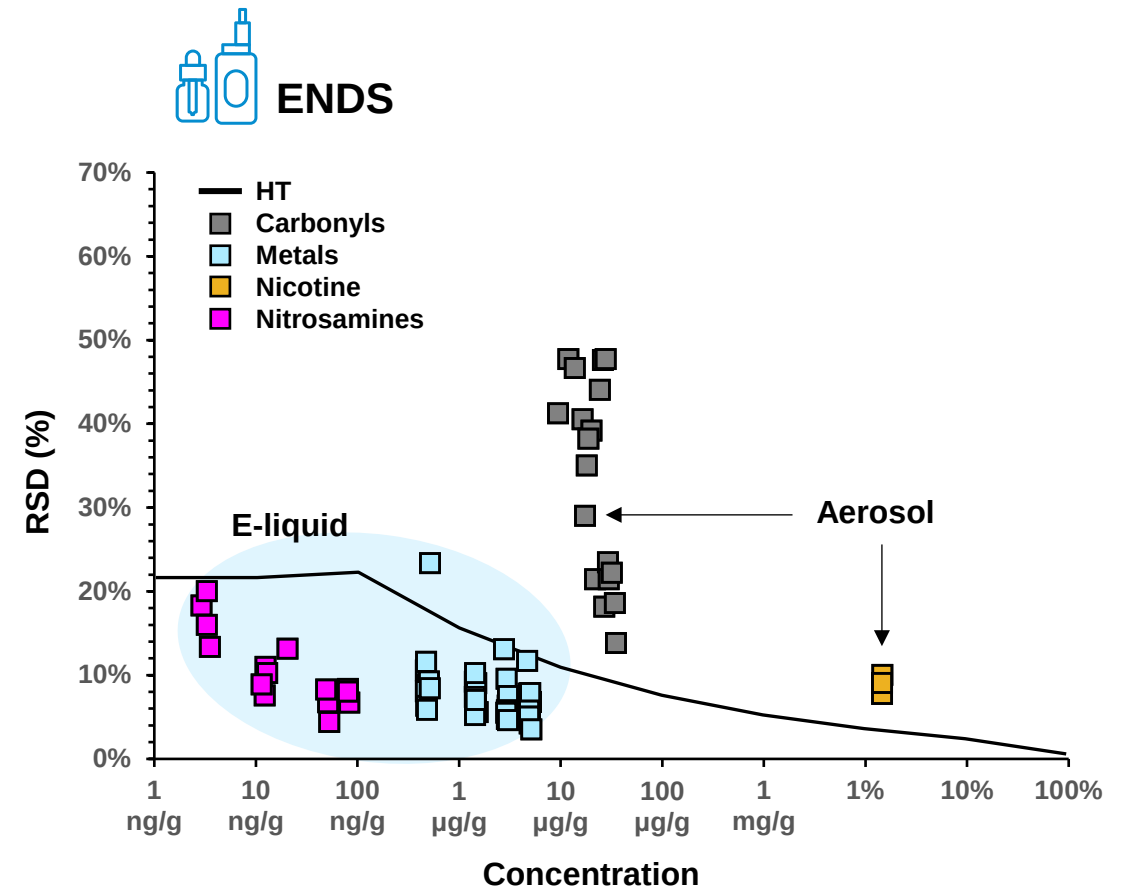
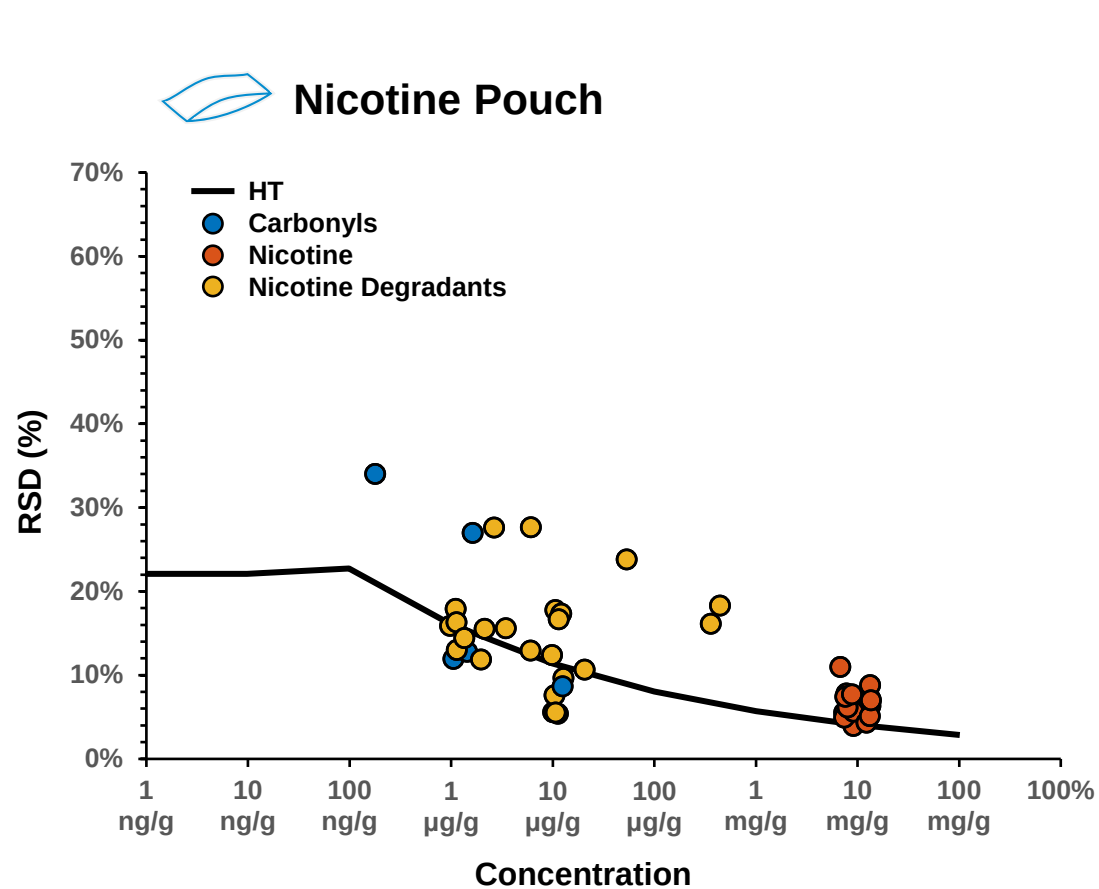
Smoke-free Product Chemical Analysis Analytes

Product	Analyte Type	Analytes	Source
Nicotine Pouch			
	Carbonyls	Formaldehyde, Acetaldehyde	TTPA-284-1-CTR
	Nicotine	Nicotine	ISO/FDIS 21114, TTPA-284-1-CTR
	Nicotine Degradants	Anatabine, β -Nicotyrine, Cotinine, Myosmine, Nicotine-N'-Oxide, Nornicotine	CRM 105
Electronic Nicotine Delivery Systems (ENDS)			
E-liquid			
	Nitrosamines	NAT, NAB, NNK, NNN	CRM 102
	Metals	Arsenic, Cadmium, Chromium, Copper, Iron, Lead, Nickel, Silver, Tin, Zinc	CRM 98
Aerosol			
	Nicotine	Nicotine	EVAP-381-CTR
	Carbonyls	Acetaldehyde, Formaldehyde	EVAP-127-2-CTR



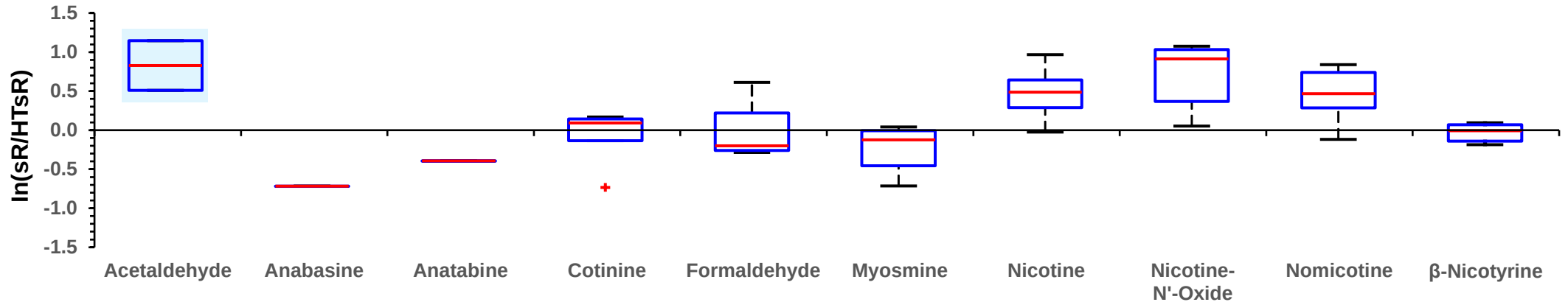
Smoke-free Product Reproducibility Standard Deviations

Departures from HT are directional and sort by product category

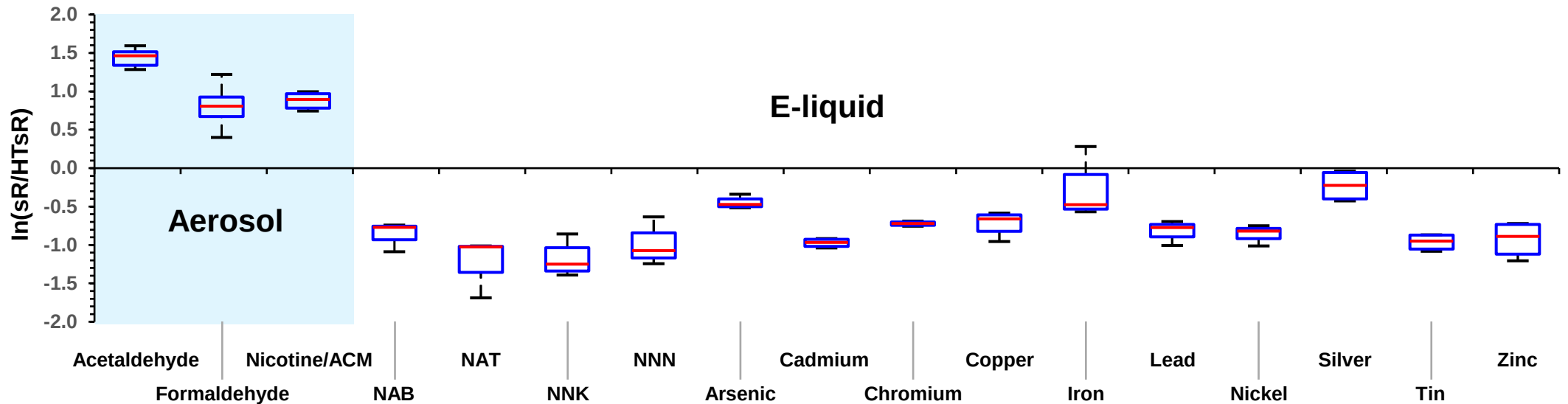


Observed Performance Frequently Differs From HT Expectations

Nicotine Pouch



ENDS



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Smoke-free Products – Why HT Deviations Occur

Smoke-free product testing adds aerosol generation and product heterogeneity – variability beyond what HT's reference-material studies reflect

Sources of Additional Variability

Aerosol generation /
collection

Sample heterogeneity

Near-LOQ behavior

Extraction efficiency

Matrix effects

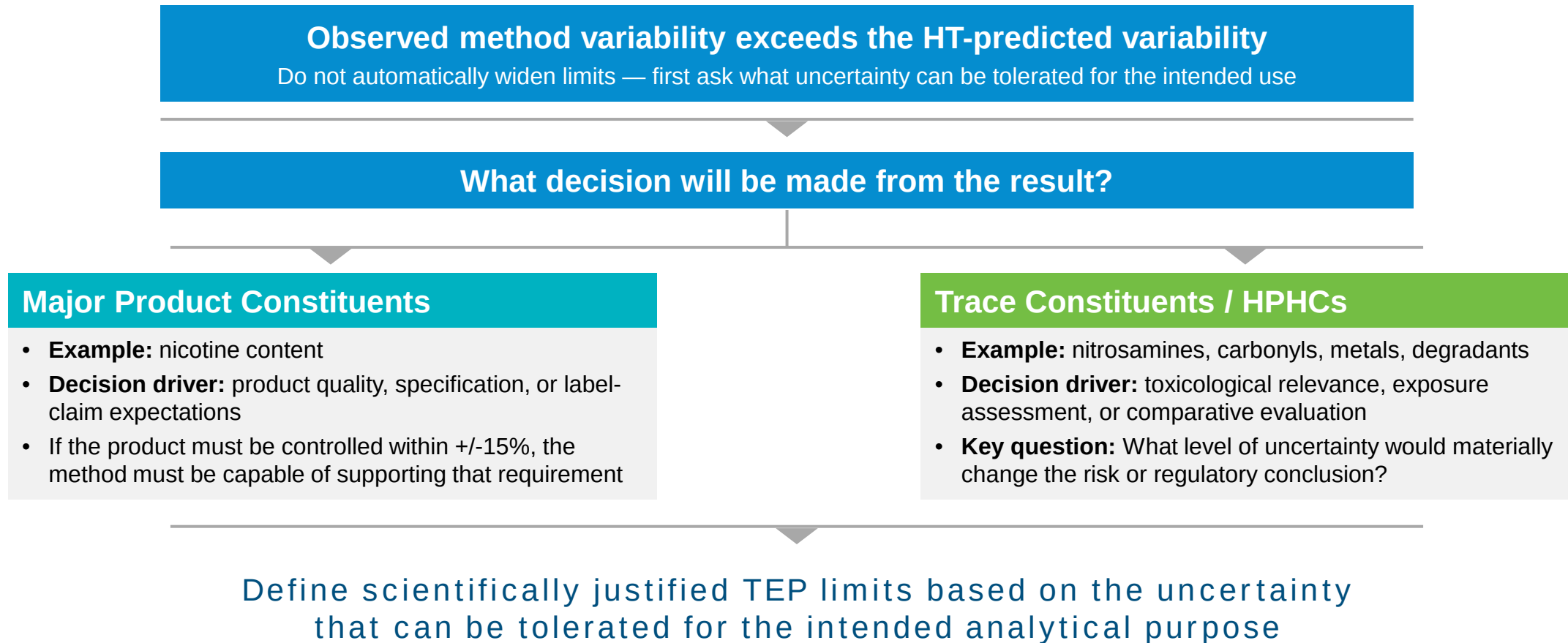


HT-based limits may not accurately reflect achievable method performance for some smoke-free product analytes



When HT & Observed Performance Differ, Fitness-for-Purpose Should Drive Acceptance Criteria

HT provides a benchmark – The final criterion should support the decision made from the analytical result





Key Takeaways

- ✓ Horwitz-Thompson provides a useful starting point for concentration-dependent estimates of reproducibility
- ✓ Smoke-free product methods often deviate from HT expectations with aerosol reproducibility at ~4x above HT, pouch reproducibility ~1.6x above and e-liquid analytes below
- ✓ Base limits on the intended use, then evaluate TEP against them





THANK YOU!

