Sniffing Out the Standards: Making Sense of Evolving Nasal Spray Testing

From Regulatory Guidance to Real-World Practice

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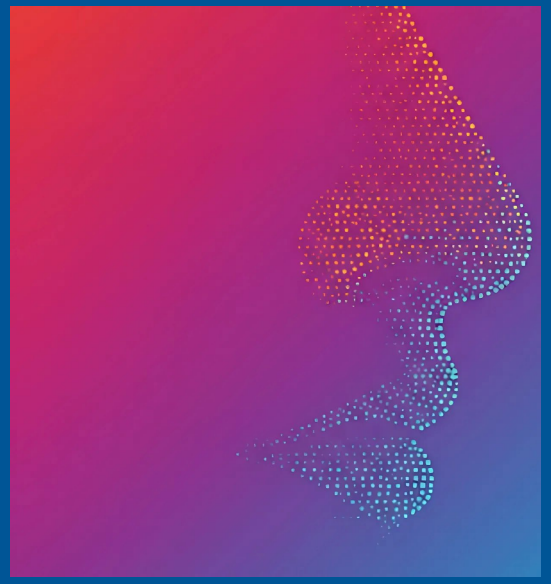
NASAL INNOVATION FORUM

IPAC-RS Event
Friday, September 19th

Agenda

- The Growing Importance of Nasal Delivery
- Regulatory Landscape: Global & Evolving Standards
- Making Sense of the Standards
  (What They Really Mean in Practice)
- Case Studies & Special Considerations
  (PBE vs. ABE, Device Testing, Actuation)
- Ensuring Success: From Method Validation to Spec Setting
- Looking Forward: Pain Points, Unmet Needs &
  Next-Gen Testing Approaches
- Key Takeaways

The Growing Importance of Nasal Delivery



- Growing importance of nasal drug delivery in therapeutic innovation – anticipated $12B+ growth over the next 10 years[1]
- Increased prevalence of respiratory disease and shift toward non-invasive drug delivery methods
- North America and EU hold majority market share
- Regulatory standards and expectations continue to evolve as technological advancements are made, and innovation solutions are developed

[1]https://www.futuremarketinsights.com/reports/nasal-spray-market

Regulatory Overview

U.S FDA

- *Spray and Inhalation Solution, Suspension, and Spray Drug Products-Chemistry, Manufacturing, and Controls Documentation - July 2002*
- *Bioavailability and Bioequivalence Studies for Nasal Aerosols and Nasal Sprays for Local Action -April 2003 DRAFT*
- *48 Product Specific Guidance – All in DRAFT*

USP General Chapters

- *USP <5> Inhalation and Nasal Drug Products—General Information and Product Quality Tests - Aug 2023*
- *USP <601> Inhalation and Nasal Drug Products: Aerosols, Sprays, and Powders—Performance Quality Tests - May 2024*

EMEA

- *Guideline on the pharmaceutical quality of inhalation and nasal medicinal products - to be effective as of February 2026*

EP General Chapters

- *Nasal Preparations (Ph.Eur. 12.0/0676)*
- *Preparations for Inhalation (Ph. Eur. 12.0/0671)*

What the Standards Really Mean?

- Breaking down key regulatory testing requirements
- For generics, passing Q1/Q2 doesn’t guarantee equivalent spray characterization performance
- Timing of tests in development – why early-phase characterization matters

US FDA Regulatory Requirements

Drug Product Characterization Studies (During Development)	Specifications for the Drug Product (Release)	Stability
Priming and Repriming in Various Orientations	Description	Description
Effect of Resting Time	Identification	Assay
Temperature Cycling	Assay	Impurities and Degradation Products
In Vitro Dose Proportionality	Impurities and Degradation Products	Preservatives and Stabilizing Excipients Assay
Cleaning Instructions	Preservatives and Stabilizing Excipients Assay	Pump Delivery
Device Robustness	Pump Delivery	Spray Content Uniformity (SCU)
Effect of Dosing Orientation	Spray Content Uniformity (SCU)	Spray Pattern
Profiling of Sprays Near Container Exhaustion	Spray Pattern and Plume Geometry	Droplet Size Distribution
Effect of Storage on the Particle Size Distribution	Droplet Size Distribution	Particle Size Distribution (Suspensions)
Plume Geometry	Particle Size Distribution (Suspensions)	Particulate Matter
Photostability	Particulate Matter	Microbial Limits
Preservative Effectiveness and Sterility Maintenance	Microbial Limits	Weight Loss
Stability of Primary (Unprotected) Package	Net Content	Leachables
	pH	pH
	Osmolality	Viscosity
	Viscosity	

EU Regulatory Requirements

https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-pharmaceutical-quality-inhalation-nasal-medicinal-products-revision-1_en.pdf

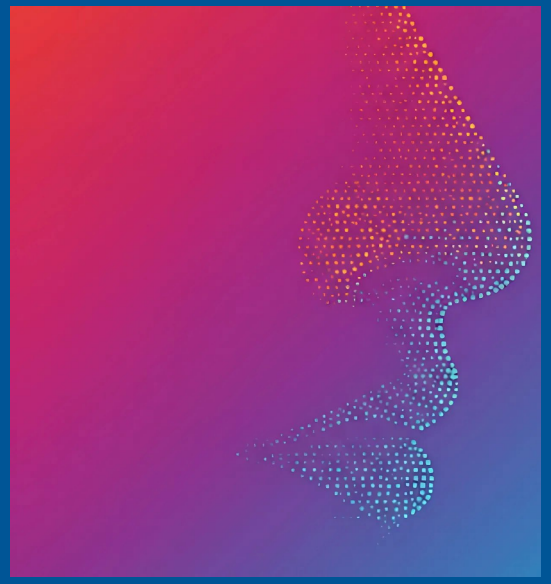


Table 5.2.1. Pharmaceutical development studies for nasal medicinal products.

Pharmaceutical development study	Pressurised metered-dose nasal spray	Nasal powders, device-metered		Nasal liquids			
		Single-dose	Multi-dose	Single-dose drops	Multidose drops	Single-dose spray	Non-pressurised multidose metered-dose spray
(a) Physical characterisation	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(b) Minimum fill justification	Yes	No	Yes	Yes	Yes	Yes	Yes
(d) Extractables / leachables	Yes	No	No	Yes	Yes	Yes	Yes
(f) Particle / droplet size distribution	Yes	Yes	Yes	No	No	Yes	Yes
(g) Uniformity of delivered dose	Yes	Yes	Yes	No	No	Yes	Yes
(j) Actuator / nasal applicator deposition	Yes	Yes	Yes	No	No	Yes	Yes
(l) Shaking requirements	Yes[a]	No	No	Yes[a]	Yes[a]	Yes[a]	Yes[a]
(m, n) Initial & re-priming requirements	Yes	No	No	No	No	No	Yes
(o) Cleaning requirements	Yes	No	Yes	No	Yes	No	Yes
(p) Low temperature performance	Yes	No	No	No	No	No	No
(q) Performance after temperature cycling	Yes	No	No	No	No	Yes	Yes
(r) Effect of environmental moisture	Yes	Yes	Yes	No	No	No	No
(s) Robustness	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(t) Delivery device development	Yes	Yes	Yes	Yes	Yes	Yes	Yes
(u) Preservative effectiveness / efficacy	No	No	No	No[b]	Yes[c]	No[b]	Yes[c]
(x) Spray pattern / plume geometry	Yes	Yes	Yes	No	No	Yes	Yes

[a] For suspensions.
[b] Single use formulations should preferably be preservative free, but if a preservative is present, it should be adequately justified.
[c] If a preservative is present.

Additional Special Considerations

Unit-dose vs. bi-dose devices:

- Actuation force

Multi-Dose:

- One-time studies – end of life, priming/repriming, in-use study

Component Testing:

- Incoming QC Requirement
  - Challenges with avoiding Release testing even when component QC is robust
- Repeatability Testing

Population Bioequivalence (PBE) *versus* Average Bioequivalence (ABE)

ASPECT	PBE	ABE
Primary Focus	Compares **mean and variability** (spread) between Test and Reference.	Compares **mean PK parameters** (Cmax, AUC) between Test and Reference.
Statistical Basis	Statistical criterion incorporates both mean differences and variance differences.	90% CI for Test/Reference mean ratio must be within 80–125%.
Variability Consideration	Explicitly accounts for differences in variability between products.	Ignores differences in variability between products.
When Used	USA	EU
Goal	Ensure products have similar **average** performance **and** similar **distribution** of responses.	Ensure products have similar **average** performance.

Best Practices in Spray Characterization

Development of spray characterization methods are essential, but complex

“Weight of Evidence” approach: Regulatory expectation for robustness and reproducibility of in vitro methods

Method Validation and Setting Specifications

Spray Actuation Content – Key Considerations

Critical Role of Actuation Parameters

- Stroke length, speed, and consistency directly affect spray output.
- Under- or over-stroking can cause deviations, particularly at end-of-life doses.

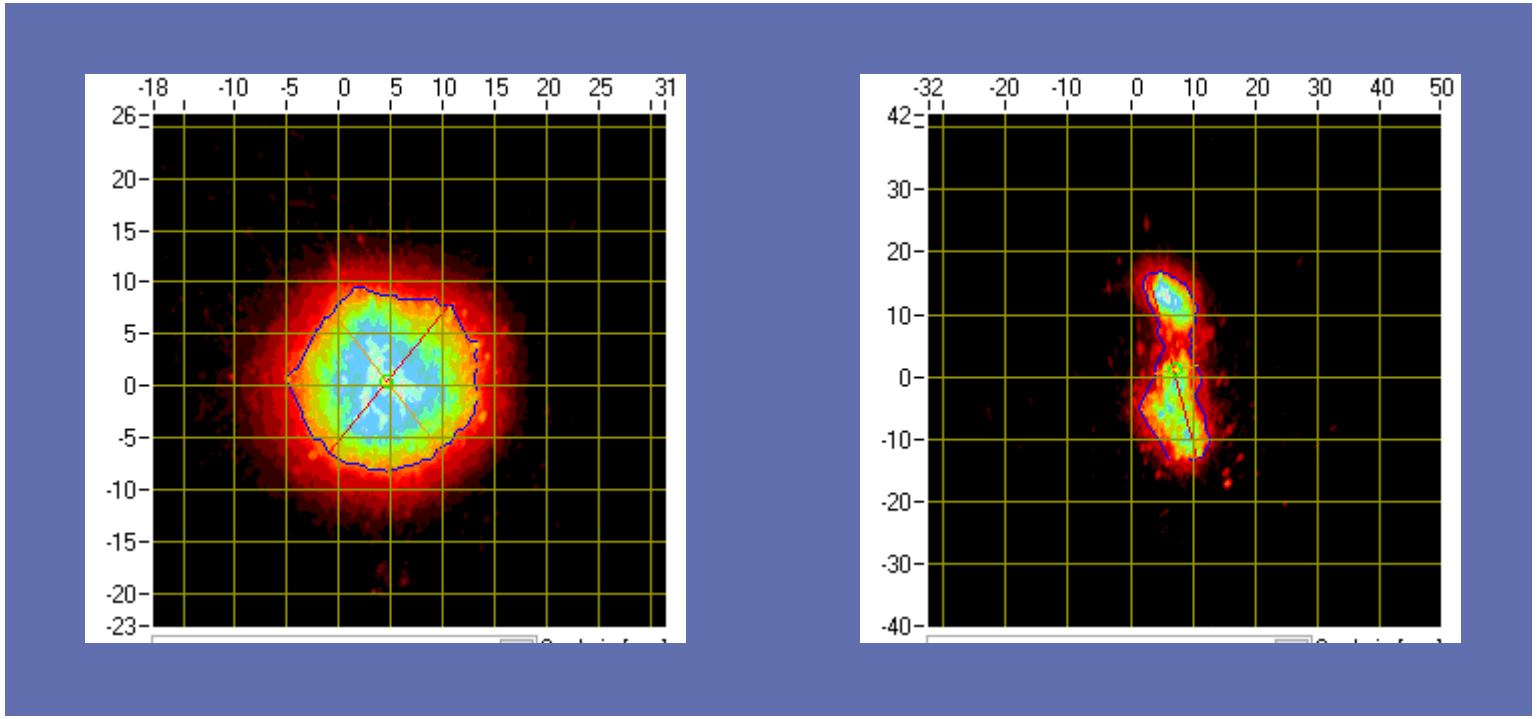
Industry Confusion:

- Current **USP <601> guidance** and **Product-Specific Guidances (PSGs)** are not fully aligned.

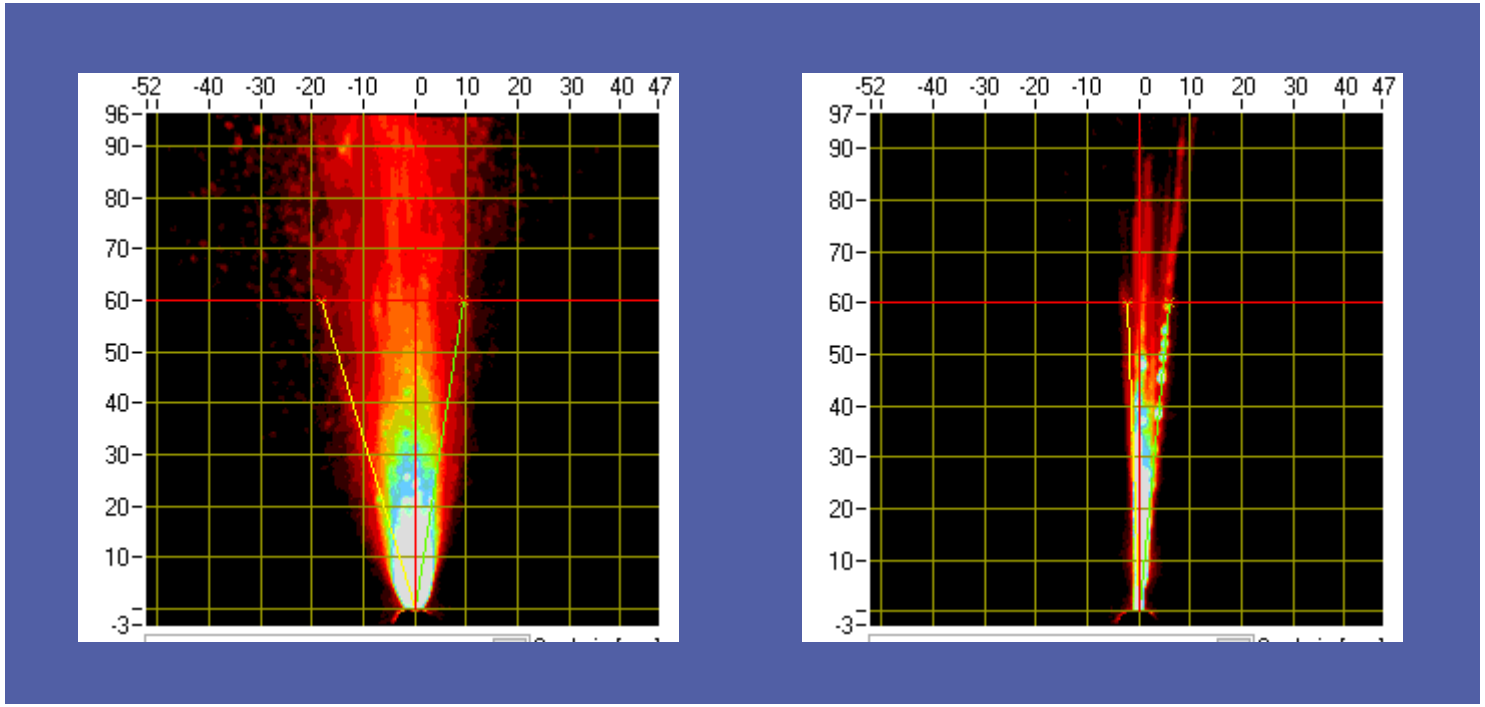
Method Validation is Essential:

- **Prove your method**: demonstrate reproducibility, accuracy, and robustness.

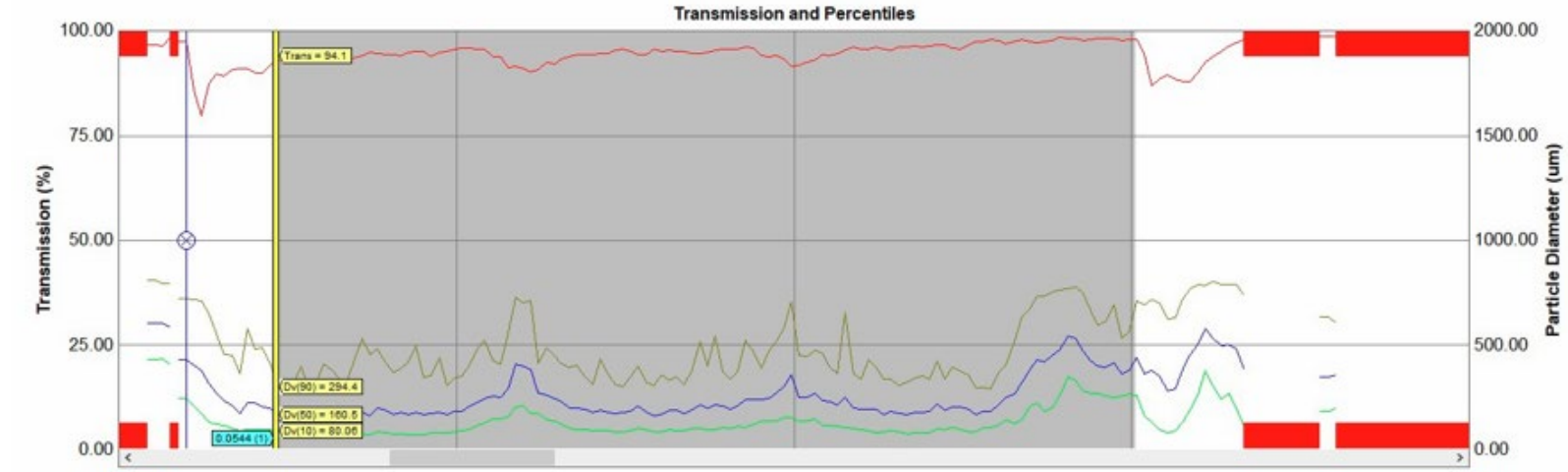
Acceptable vs. Out of Trend – Spray Pattern



Acceptable vs. Out of Trend – Plume Geometry



Acceptable vs. Out of Trend – DSD



Warning ⚠

If this occurs the measurement data will continue to be analysed and a warning message, denoted by an exclamation mark (!), will be displayed in the Measurement parameters record view.

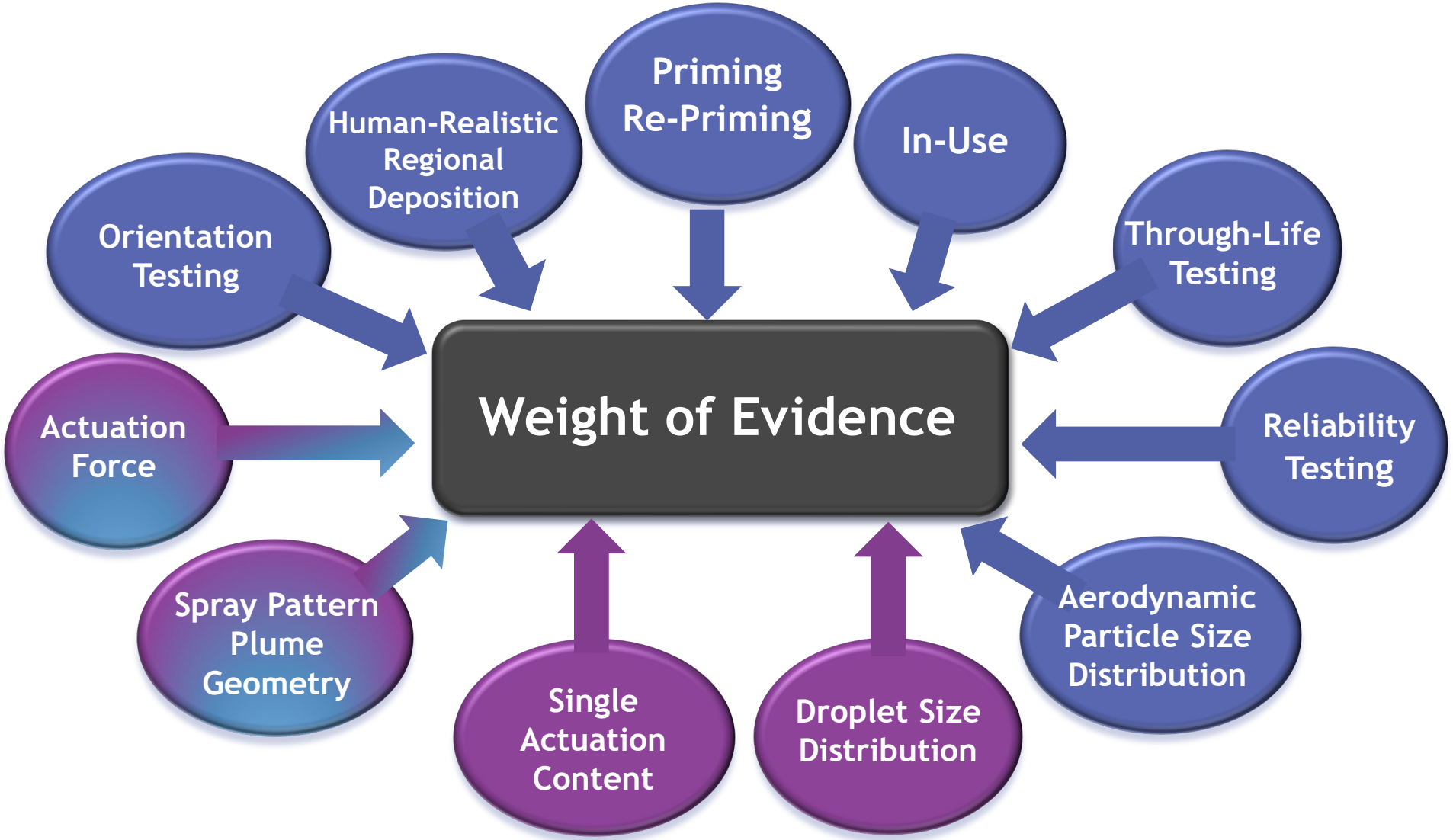
The reason for the warning will be displayed at the bottom of the measurement parameters window.

Error ⚠

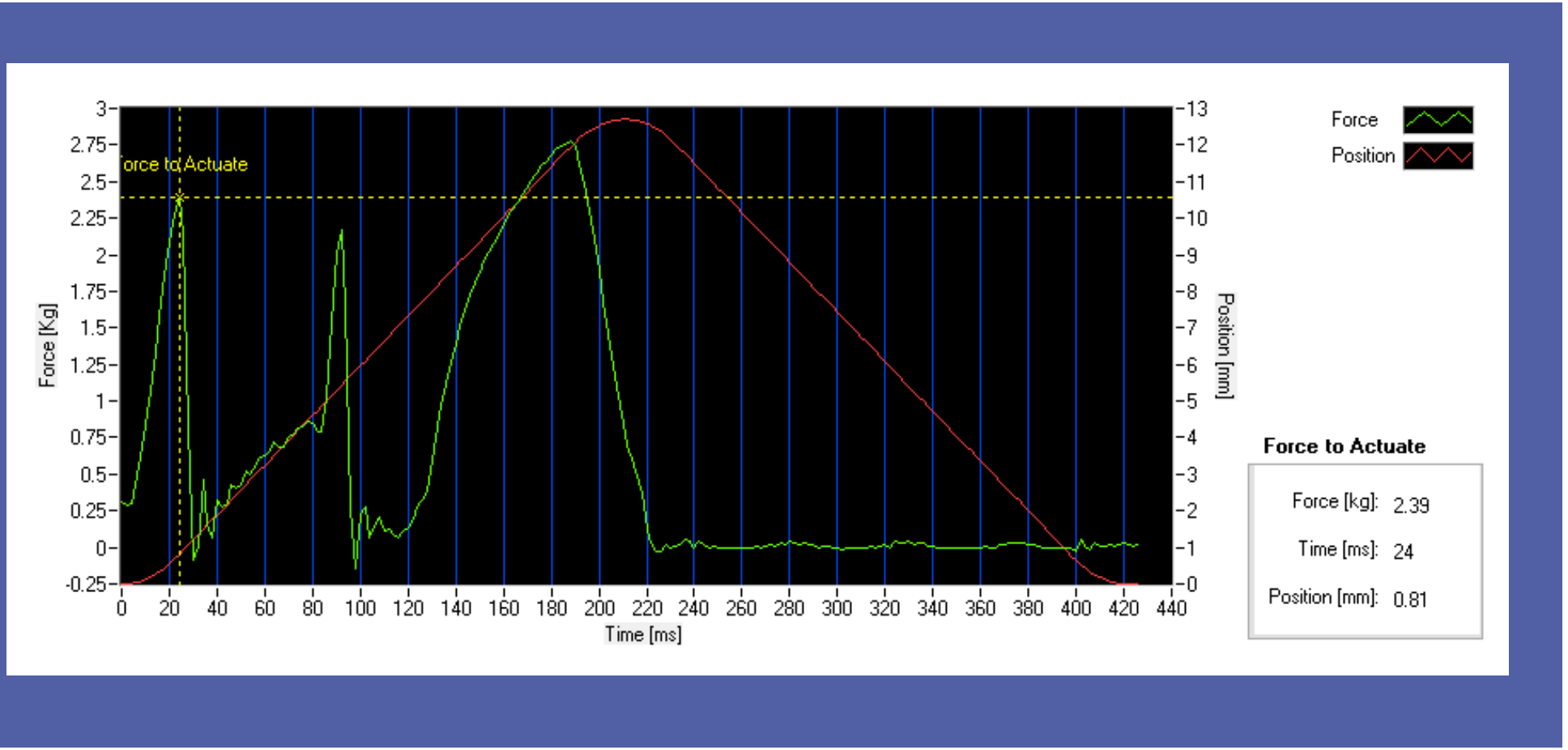
If this occurs the measurement data will not be analysed and red bars are displayed in **place of** the expected results in the Particle Size History view. Messages are also displayed in the Measurement parameters window, where they are denoted by three exclamation marks (!!!).

The reason for the warning will be displayed at the bottom of the measurement parameters window.

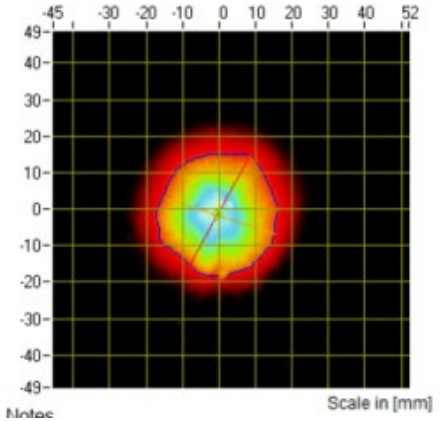
Weight of Evidence



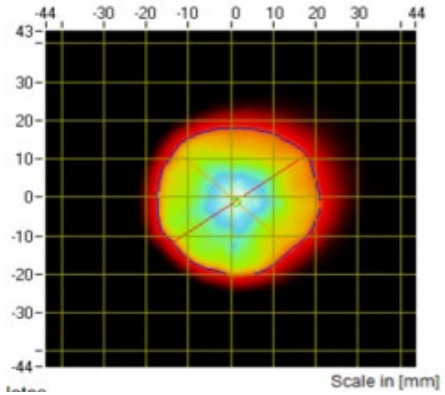
Force to Actuate



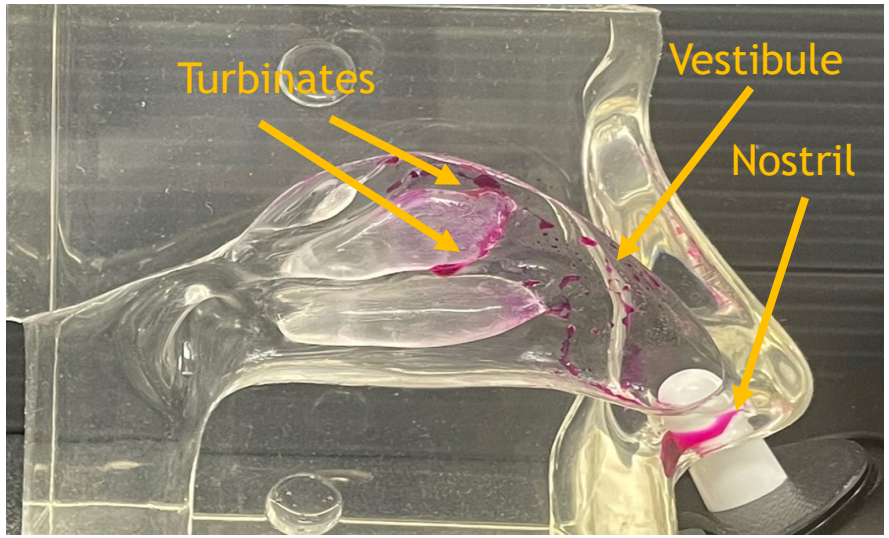
0%G Spray Pattern & Deposition

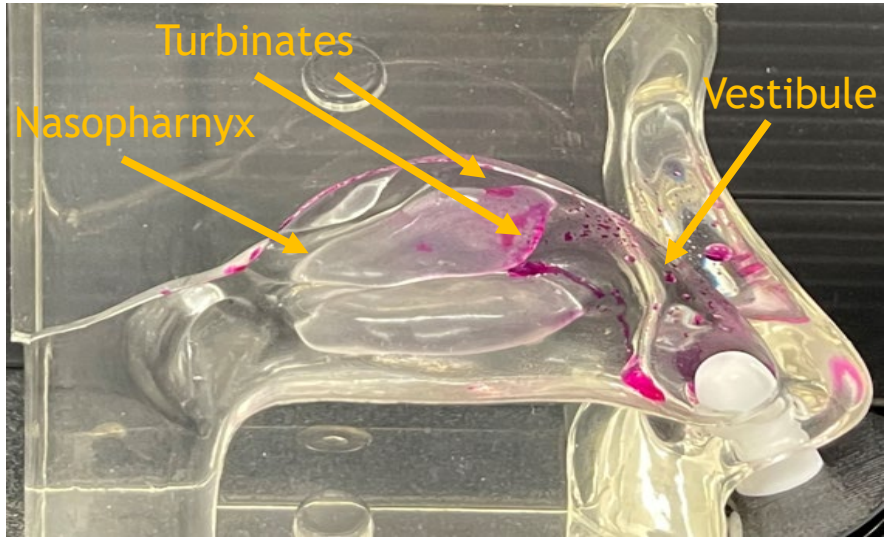


Dmax: 34.91mm Ovality: 1.085



Dmax: 39.65mm Ovality: 1.058

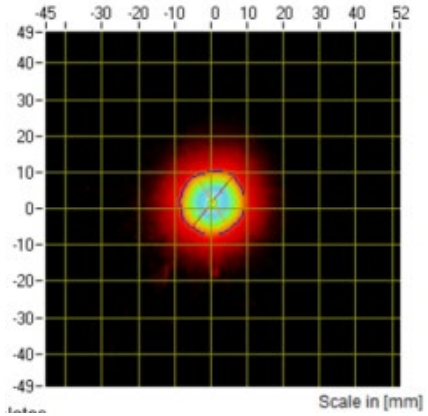




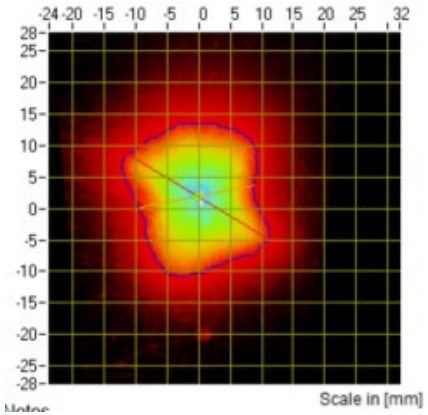
Method 1 - Vel: 70mm/s Accel: 5000mm/s²	
LOCATION	DEPOSITION
VESTIBULE	✘
TURBINATES	✘
NASOPHARNYX	
RUN OUT NOSTRIL	✘

Method 2 – Vel: 130mm/s Accel: 8000mm/s²	
LOCATION	DEPOSITION
VESTIBULE	✘
TURBINATES	✘
NASOPHARNYX	✘
RUN OUT NOSTRIL	

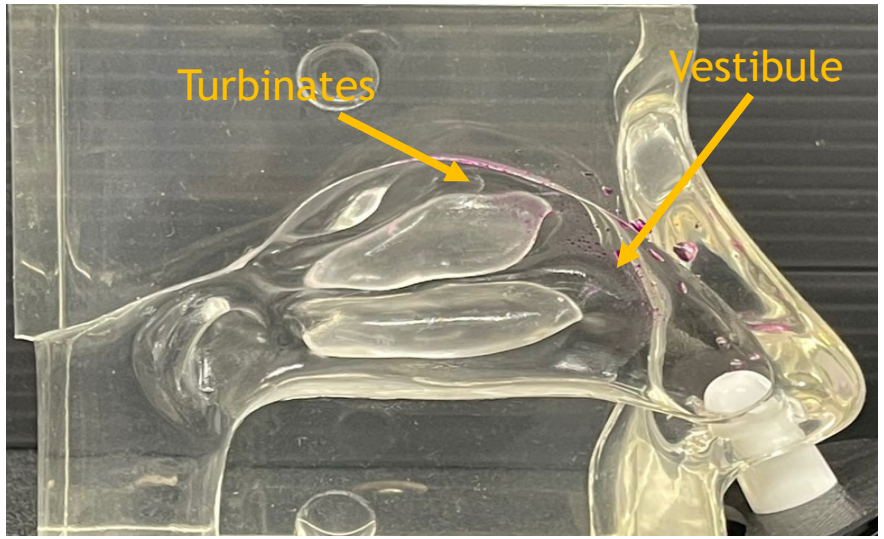
60%G Spray Pattern & Deposition

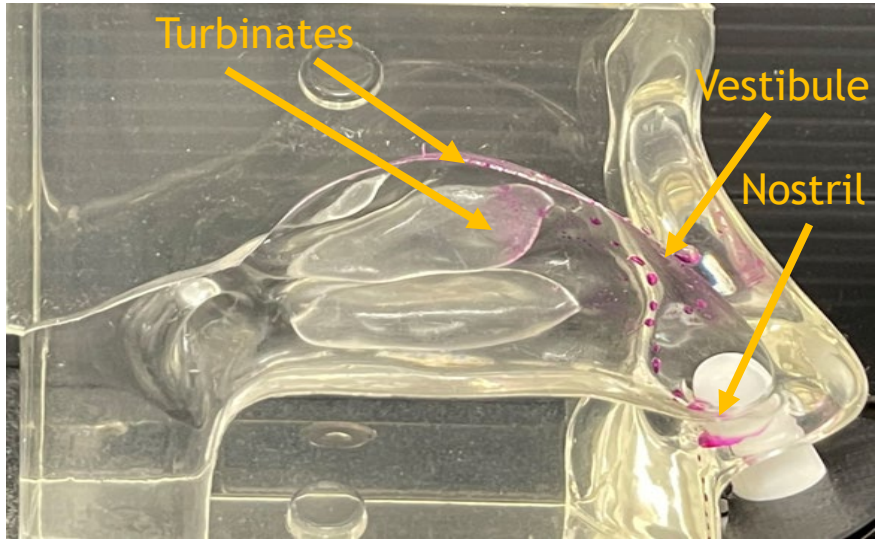


Dmax: 19.05mm Ovality: 1.108



Dmax: 26.56mm Ovality: 1.438

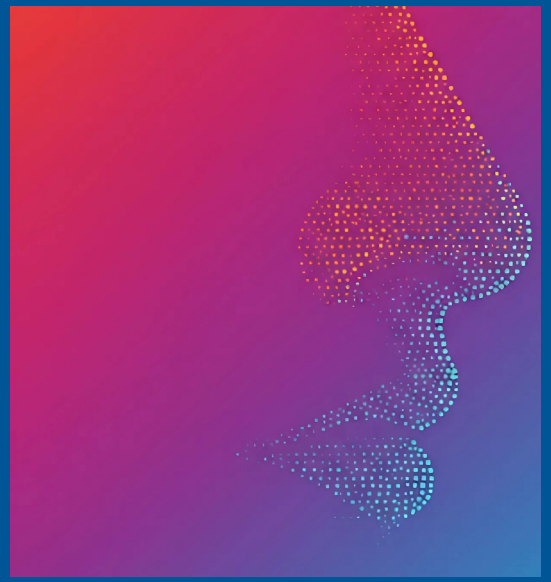




Method 1 - Vel: 70mm/s Accel: 5000mm/s²	
LOCATION	DEPOSITION
VESTIBULE	✘
TURBINATES	✘
NASOPHARNYX	
RUN OUT NOSTRIL	

Method 2 - Vel: 130mm/s Accel: 8000mm/s²	
LOCATION	DEPOSITION
VESTIBULE	✘
TURBINATES	✘
NASOPHARNYX	
RUN OUT NOSTRIL	✘

Validation of Spray Characterization Methods



Robustness - Method performs reliably under small, deliberate variations in conditions.

Qualification - Demonstrates the method is suitable and fit for its intended purpose.

Repeatability – Produces consistent results when tested under the same conditions.

Intermediate Precision – Confirms reproducibility across different days, analysts, or instruments.

From Data to Decisions

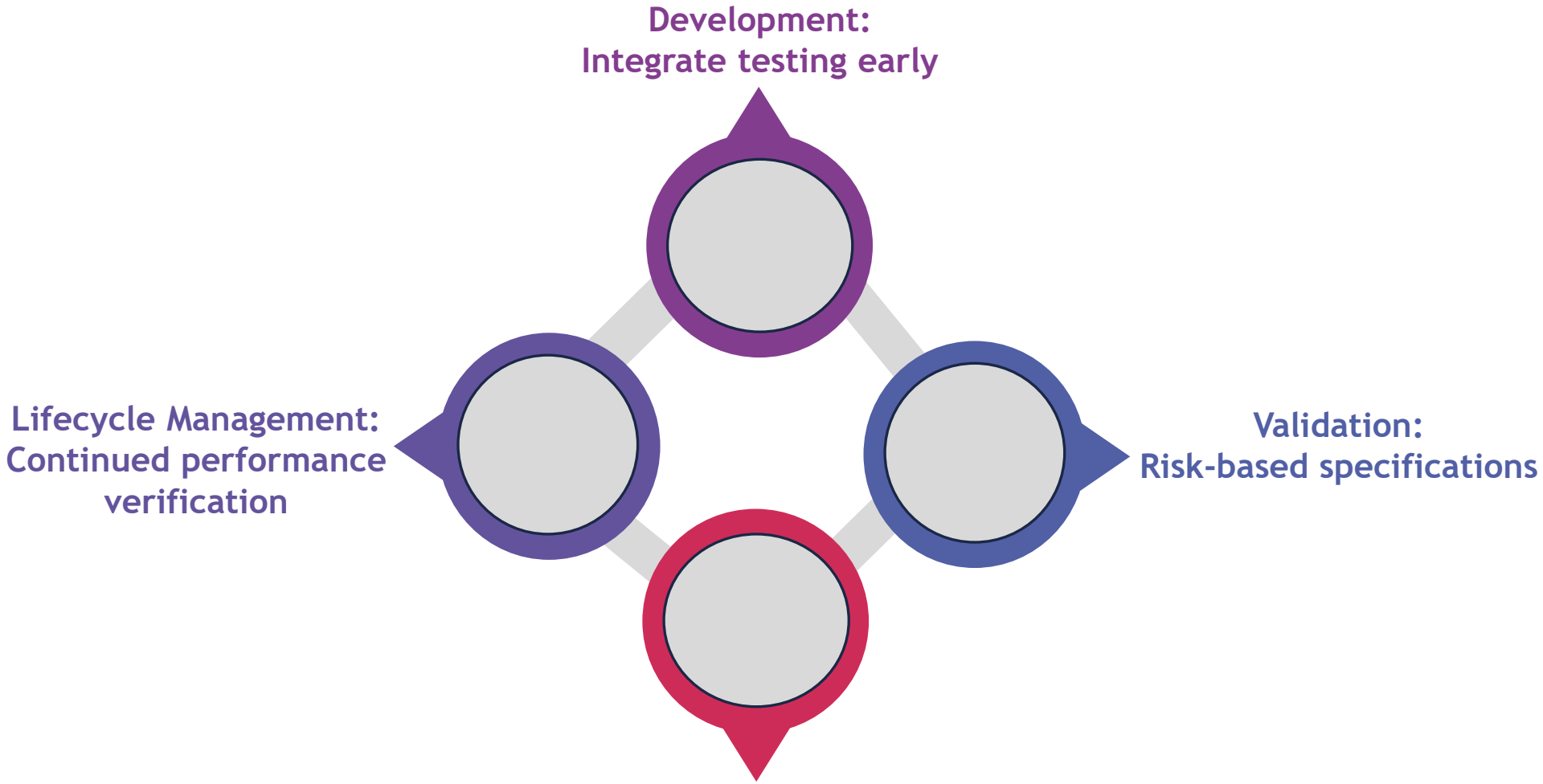
Setting Sample Sizes and Specifications for Nasal Spray Products

Understand Variability → Define Sample Size & Tiering → Select Statistical Method → Justify via Risk & Data

Key Considerations
Account for inherent product variability
Plan for occasional outliers (“rogue devices”)
No single pass/fail rule: regulators expect a science- and risk-based justification
Tier 1 vs. Tier 2 testing: balance number of devices and replicates per device (especially for multi-dose)
Critical Quality Attributes (CQAs): Specs should be tied to attributes that impact clinical performance

Options for Specifications
Tolerance Intervals (to capture a % of future data)
Percentile-based limits (e.g., 95th % bounds)
Clinical relevance anchor (link to PK/PD or deposition performance)
Historical batch data (development + stability justification)
Risk-based acceptance criteria (tighter for CQAs, wider for non-critical attributes)

Ensuring Success from the Development Lifecycle



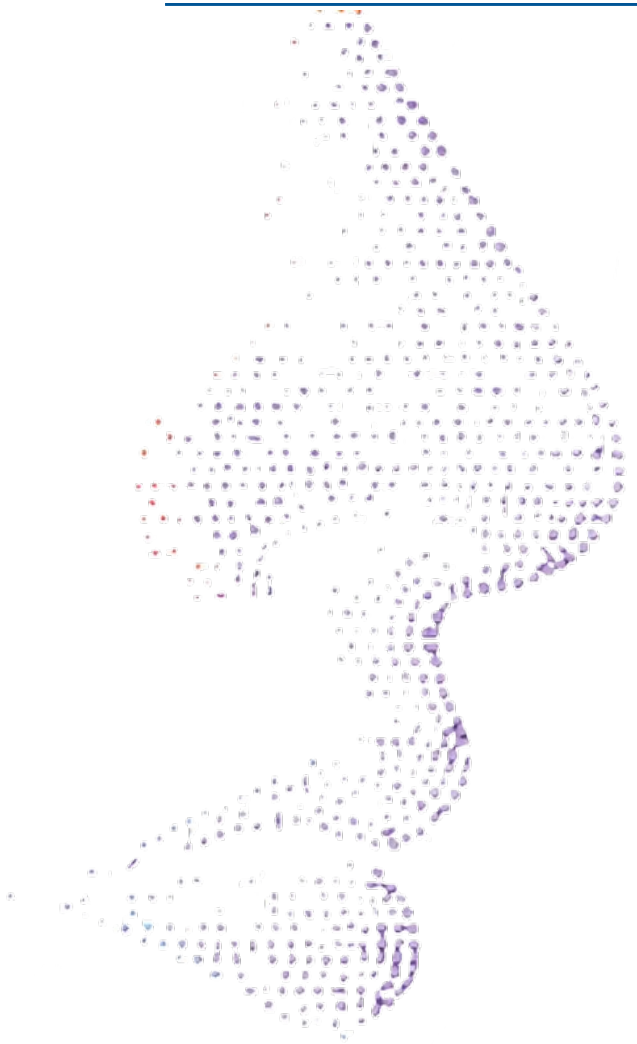
Industry Pain Points & Unmet Needs

Gaps between regulatory guidances and real-world feasibility

Guidance's staying in *Draft* for decades – "Living Document" reality

Not all compendial aspects are reflected in FDA PSGs

Nasal Spray Testing
Next-Generation Approaches



Patient-Centered Testing

Leverage human-realistic actuation profiles that reflect true patient use

Expand physiologically relevant nasal cast models for predictive performance

Integrated Strategies

- Combine in vitro, in silico, and in vivo methods for holistic understanding
- Anticipate and align with evolving regulatory standards

Collaborative Innovation

Strengthen partnerships between industry, regulators, and suppliers

Share data/methods to harmonize best practices and accelerate progress

Key Takeaways

START SPRAY CHARACTERIZATION EARLY – DON'T WAIT UNTIL VALIDATION STAGE

KEEP TESTING APPROACHES ADAPTABLE TO EVOLVING GUIDANCE

VALIDATE CRITICAL METHODS LIKE SP/PG FOR REGULATORY CONFIDENCE

ENGAGE WITH FORUMS LIKE **IPAC-RS** TO HELP SHAPE STANDARDS

Thank you for attending!

Questions?