

Experimental glimpse on micro-volume metrology for industrial standards

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Motivation

Micro-volume measurements are crucial in various industries, particularly pharmaceutical and biotech, where precision can impact product safety, efficacy, and quality. Micro-volume pipettes are essential tools used to transfer and measure tiny liquid volumes with high precision, typically in the range of microliters (μL) or nano-liters (nL). Calibration of these instruments ensures accurate and consistent measurements, reducing risks of errors in sensitive processes such as drug development, manufacturing, and testing.

Challenges in micro-volume measurements include inherent instrument precision limits, viscosity and surface tension, evaporation, and user error. Proper training is essential for minimizing user errors and ensuring accurate measurements in these critical processes. Accurate pipetting directly influences quality control, product consistency, and compliance with industry regulations.

Pipette calibration involves selecting a reference material, using the gravimetric method to measure the mass of the dispensed liquid, and testing at different volumes to ensure accuracy across their entire range. The importance of pipette calibration lies in regulatory compliance, product consistency, quality control, reducing human error, traceability, and accountability. Regular calibration ensures that pipettes meet required specifications for accuracy, supports compliance with regulations set by authorities like the FDA and EMA, and ensures product consistency.

In critical industries, well-calibrated pipettes ensure traceability to recognized standards and allow for consistent comparisons between different laboratories, ensuring reproducibility of results across experiments. This study aims to determine the best way to calibrate micropipettes down to 1 microliter (μL) under specified measurement settings while identifying, examining, and correcting the sources of inaccuracy.



Clinical diagnostics using a micropipette for precise liquid sample transfer

Importance & Main Applications of Micro-Volume Measurements

Importance

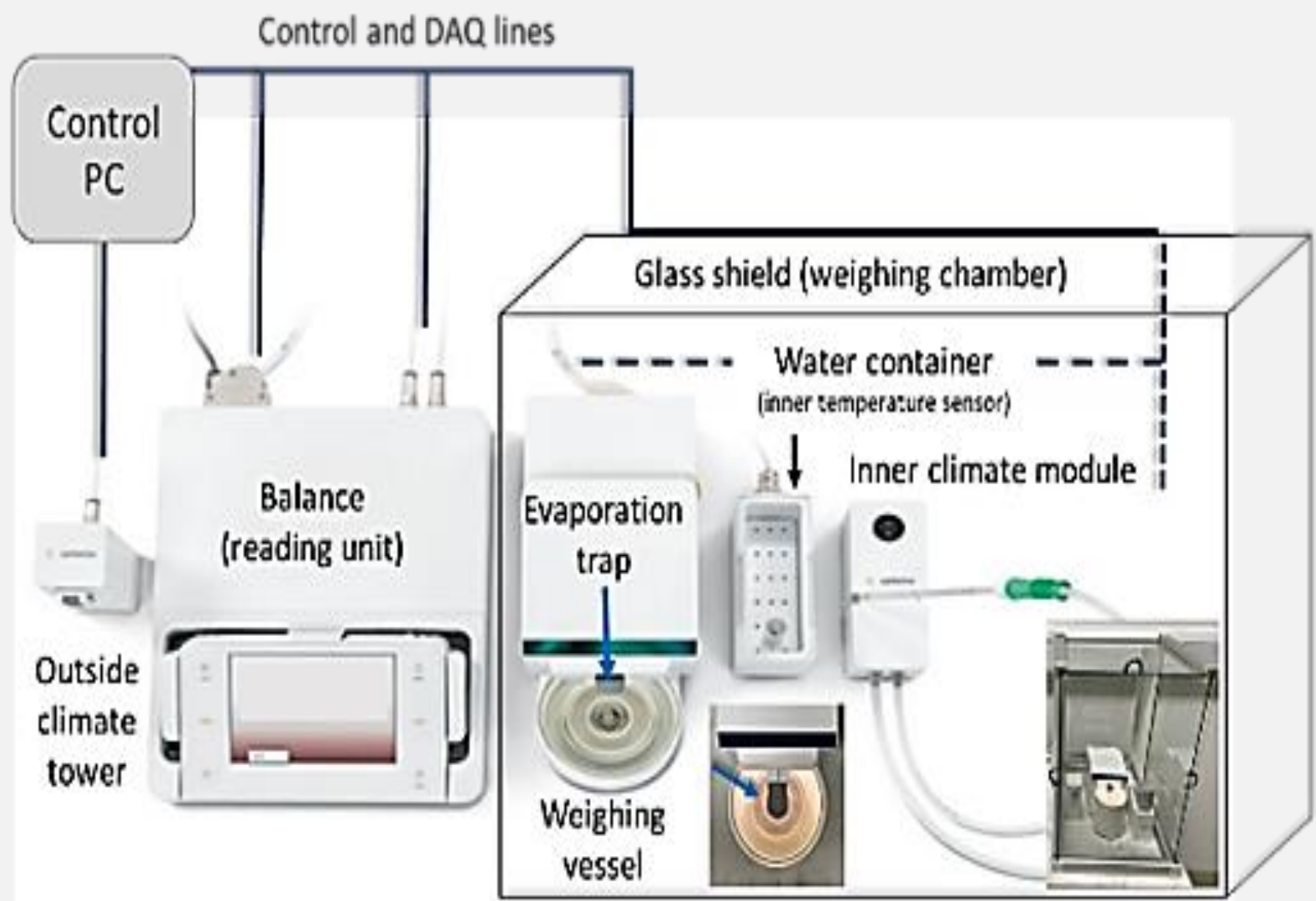
Micro-volume measurements play a crucial role in ensuring **accuracy and reliability**, particularly in **industrial and medical fields** such as **pharmaceutical and biotech industries**. **Regular calibration** ensures compliance with regulatory standards set by organizations like **FDA and EMA**, contributing to **product consistency and quality assurance**.

Moreover, precise calibration helps **reduce human errors** in manual liquid handling, as mistakes in this stage can lead to **significant measurement discrepancies** that may affect research and clinical trial results. It also ensures that all measurements **are traceable to globally recognized standards**, facilitating **reproducibility and comparison between different laboratories**.

Due to these benefits, **regular calibration** is essential for maintaining **accuracy in laboratory processes**, improving **quality control**, and minimizing **variations in results**, ultimately enhancing **data reliability** and supporting **scientific advancements** in fields such as **biotechnology and drug development**.

Vital Applications

- ❑ Drug discovery and development
- ❑ Cell culture and biotechnology
- ❑ Clinical diagnostics
- ❑ Quality control in manufacturing
- ❑ Environmental and forensic testing



Schematic of the equipment used for gravimetric calibration of micro-pipettes at NMCC

Challenges in Micro-Volume Measurements

Micro-volume measurements face several challenges that affect their accuracy and reliability, making precise control essential in industrial and medical applications. These challenges include:

Instrument Precision Limitations

Micropipettes have inherent precision limits, and minor design flaws or improper use can lead to measurement errors.

Effect of Liquid Properties

Viscosity, surface tension, and evaporation can impact the accuracy of liquid transfer, leading to discrepancies between the measured and actual volumes.

Evaporation and Environmental Changes

In extremely small volumes, rapid evaporation can reduce the measured liquid amount, especially in environments with varying temperature or humidity levels.

Human Errors

A user's skills and experience in handling micropipettes significantly influence measurement accuracy. Uneven plunger pressure or incorrect pipetting angles can result in inaccurate readings. These challenges highlight the importance of **proper training and routine calibration** to achieve accurate and consistent micro-volume measurements in critical fields such as pharmaceuticals, biotechnology, and clinical diagnostics.

Case Study: Micropipette Calibration

Importance of micropipettes in medicine, chemistry, biology, pharmacy, and genetics.

Goal: Find the best way to calibrate micropipettes to **1 μL** while identifying and correcting inaccuracies.

Development of a **mathematical model for measurement uncertainty**.

Experimental setup:

Use of **custom software, evaporation trap, and a 0.001 mg micro-balance**.

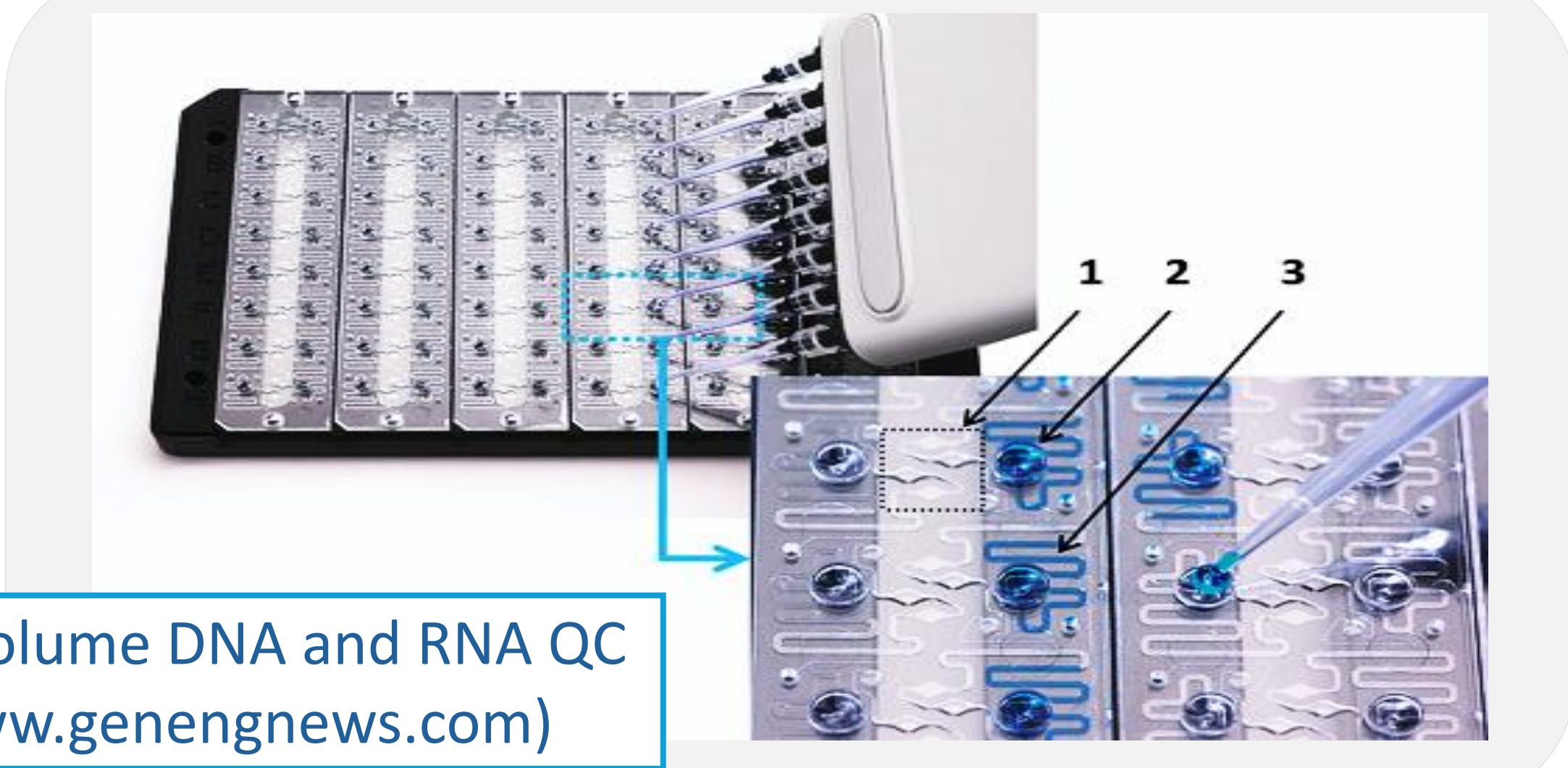
Achieved **expanded uncertainty level of 0.019 μL ($k = 2$) at 1 μL calibration** at SAS-NMCC.

Results:

Improved accuracy and consistency in micro-volume calibration.

Enhanced uncertainty budget.

Use of **GUM methods and relevant standards** for expanded uncertainty evaluation.



Standardizing Micro-volume DNA and RNA QC
(Source: <https://www.genengnews.com>)

[1] ISO 8655-6:2002 - Piston-operated volumetric apparatus -- Part 6: Gravimetric methods for the determination of measurement error

[2] Evaluation of the Accuracy of Pipetting in Clinical Laboratories

[3] Best Practices in the Use and Calibration of Micropipettes in Biological Research

[4] Techniques of Precise Volume Measurement in Analytical Chemistry

[5] Effect of Liquid Properties on Micropipette Accuracy