The Impact of Metrology on Health Care Quality and Safety: A Focus on Infusion Therapy and Diagnostic

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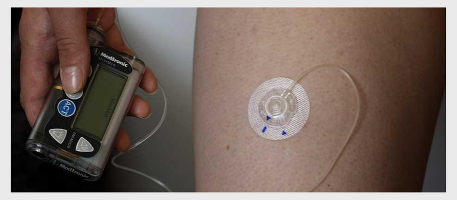
Infusion technology

Metrology, the science of measurement and its applications, is crucial for healthcare quality and safety, especially in infusion therapy and diagnostics. Vital signs like heart rate, blood pressure, and blood oxygen levels can indicate dosing errors from infusion pump flow rate adjustments in multi-infusion setups.

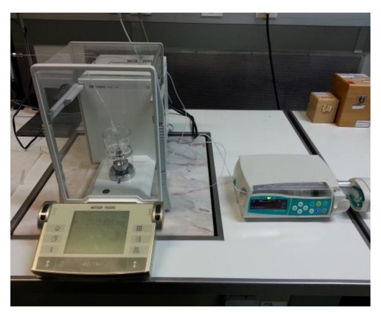
Infusion therapy, the most common drug administration method, relies on precise liquid flow. Accurate liquid dosing is essential for the safety and reliability of medical devices like dialysis machines, infusion devices, and in-vitro diagnostic systems. Infusion errors, particularly in ICUs, can have severe consequences, especially with critical drugs or low doses for premature infants. Many adverse incidents, including morbidity and mortality, are linked to inaccurate dosing.



The role of metrology in drug delivery devices

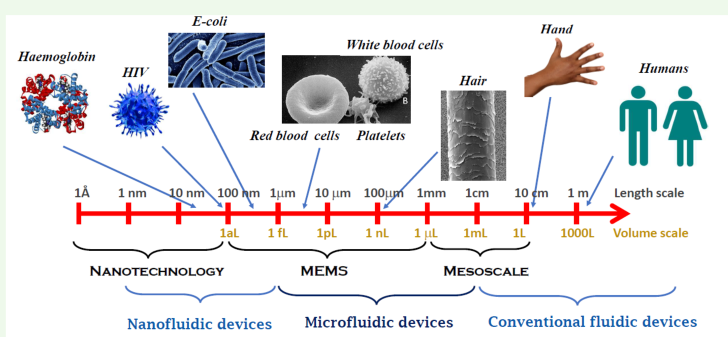
Calibration is crucial for identifying flow rate and dosage errors in multi-infusion systems. Drug delivery can vary with flow rate adjustments and setup configuration, leading to differences between actual and intended doses. Clinicians adjust medications based on vital signs, needing a clear understanding of multi-infusion impacts. Accurate infusion pump delivery is vital to avoid clinical safety risks.

Precise control of medication and fluid delivery, especially for critical drugs and other fluids, is essential. Regular calibration and maintenance of drug delivery devices ensure correct dosages, and minimize safety risks.

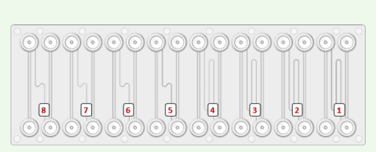


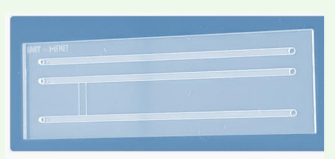
Microfluidics

The diagnostics sector is rapidly advancing, driven by the need to manage infectious diseases like COVID-19. Metrology significantly impacts the commercialization of next-generation microfluidic devices, such as point-of-care diagnostics (PoCD), lab-on-a-chip (LoC), and organ-on-a-chip (OoC).

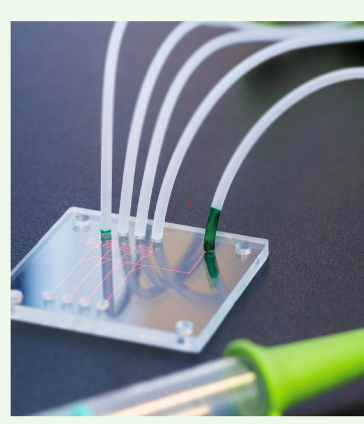


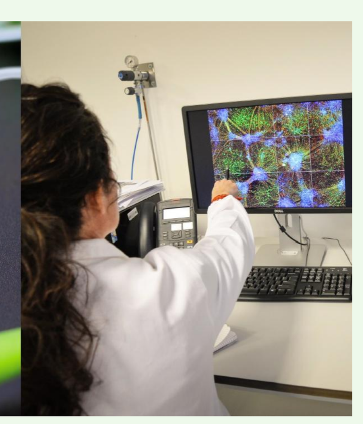
Microfluidics studies fluid behavior through microchannels and involves manufacturing devices with tiny chambers and tunnels. Organ-on-Chip replicates aspects of an organ's dynamics and responses within a non-biological platform.

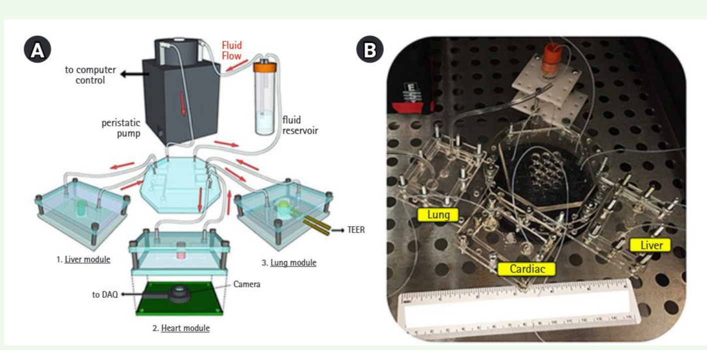




The last decade has seen phenomenal growth in the field of microfluidics. However, the quality production of microfluidic devices has largely relied on the expertise of the manufacturers, with no standardized calibration procedures or standards to streamline and accelerate production. Despite the potential impact of microfluidics on society, health, well-being and the environment, success stories are relatively rare compared to the number of laboratory developments. This gap is due to the differences between laboratory microfluidic devices (home-made chips, customized test protocols, materials not suitable for mass production) and reliable, reproducible products.

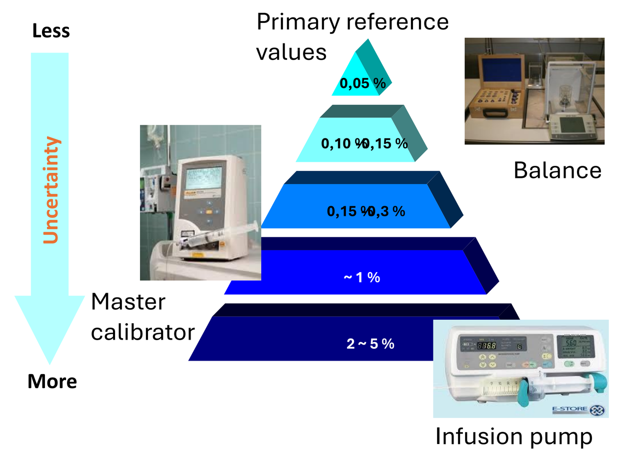






State of the art

A well-defined traceability chain ensures that drug delivery devices meet manufacturer and end user specifications. Enhanced metrological infrastructures in European National Metrology Institutes, through the EMPIR MeDD – Metrology for Drug Delivery project, have improved the safety of infusion therapy by developing reliable test methods and protocols.



Calibration methods of drug delivery devices

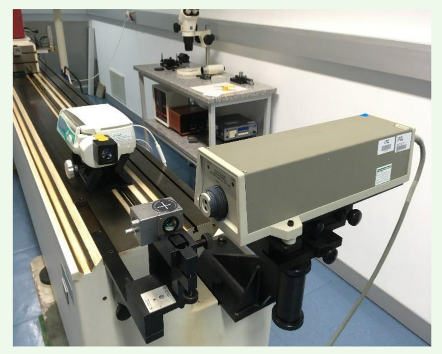
Gravimetric method

The gravimetric method is the most common for calibrating drug delivery devices, including peristaltic and syringe pumps and flow meters. Gravimetric facilities for micro flow calibrations typically include a flow generator (e.g., piston prover, syringe pump, pump and flow controller system) and a flow rate reference system realized by a weighing scale and a "stopwatch" to measure liquid mass over time.

Flow rate down to 15 nL/min with an uncertainty of of 1 % (k=2)

$$Q = \frac{1}{t_f - t_i}\left[\left((I_f - I_i) - (\delta m_{buoy})\right) \times \frac{1}{\rho_w - \rho_A} \times \left(1 - \frac{\rho_A}{\rho_B}\right) \times [1 - \gamma(T - 20)]\right] + \delta_{evap}$$

Displacement method



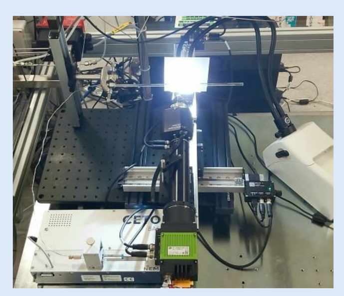
High precision syringe pumps and piston provers generate pulse-free, accurate flow rates by the displacing a piston plunger. Syringe pumps use glass or stainless steel syringes, while piston provers are mainly stainless steel. The plunger's position, speed, and the piston's inner diameter can be calibrated to ensure traceability. Length metrology uses interferometry to calibrate the plunger's position, monitoring the distance traveled by the syringe pump's pusher block over time.

Flow rates down to 1,6 nL/min with an uncertainty of 2% (k=2)

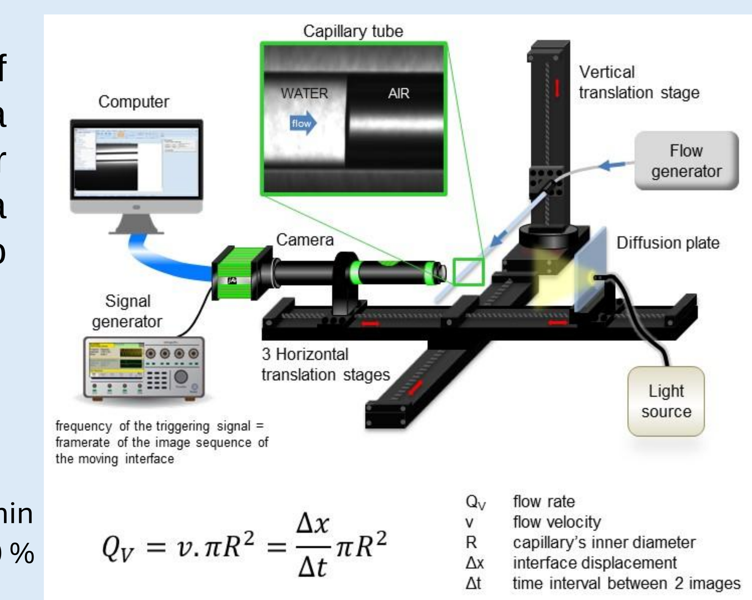
$$Q = v \times A = \frac{x_2 - x_1}{\Delta t} \times \pi r^2 = \frac{d\pi r^2}{t}$$

Front Track method

Meniscus (or front) tracking consists of measuring the displacement as a function of time of a liquid/air or liquid/liquid interface moving inside a glass capillary tube that is connected to a flow generating device.



Flow rate down to 1 nL/min with an uncertainty of 10 % (k=2)

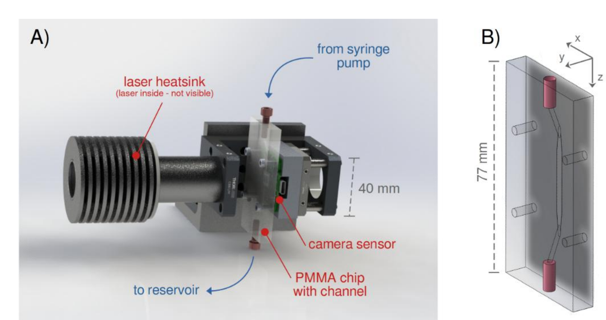


$$Q_V = v.\pi R^2 = \frac{\Delta x}{\Delta t}\pi R^2$$

Q_V flow rate
v flow velocity
R capillary's inner diameter
Δx interface displacement
Δt time interval between 2 images

Micro PIV/Micro PTV method

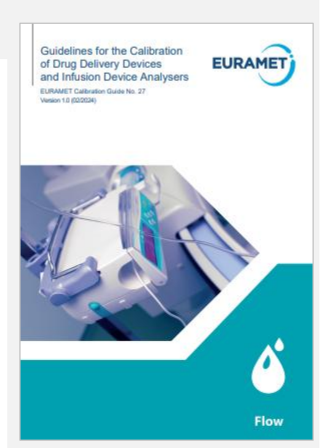
Alternative methods for micro/nano flows include Particle Tracking Velocimetry (PTV) and Particle Image Velocimetry (PIV). PTV determines flow velocity by tracking individual tracer particles across frames, while PIV calculates velocities by dividing video frames into patches and cross-correlating them in successive frames.



Methods validation

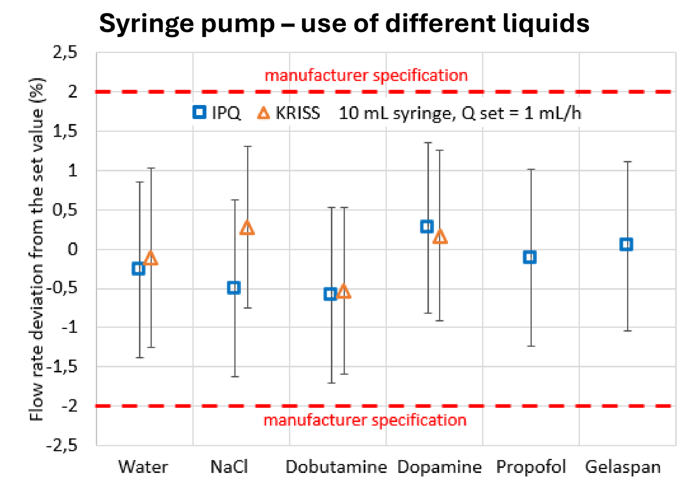
Two inter-comparison of the primary standards were performed to validate the new flow facilities. Project 1291 in 2015 and project 1508 in 2022, the results were overall consistent and let to publication of new flow CMCs by 5 different NMIs.

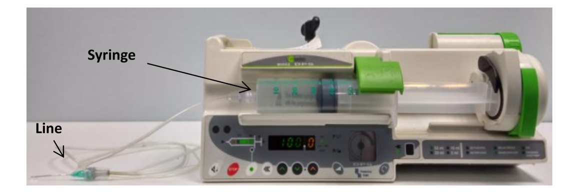
A new EURAMET guide was developed and published in May 2024 - EURAMET Calibration Guide No. 27 - Guidelines for the Calibration of Drug Delivery Devices and Infusion Device Analysers as one of the deliverables of MeDD project.

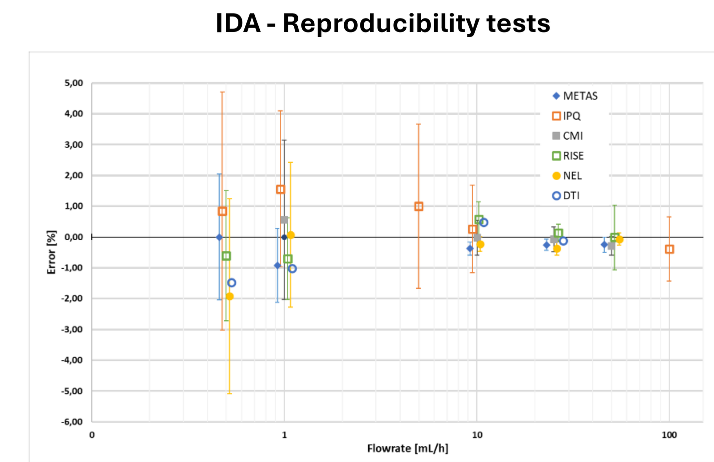


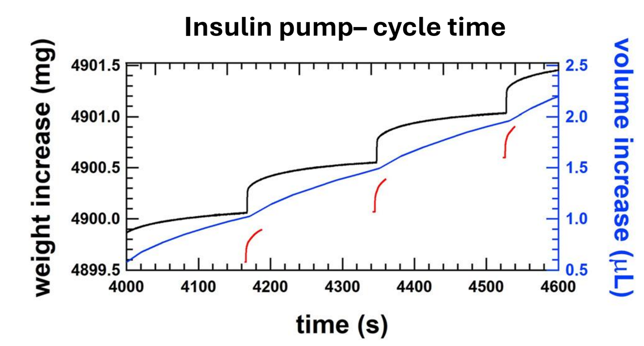
Results and research activities in drug delivery devices

After the facilities were in place it is was possible to characterize several types of drug delivery devices, like syringe pumps, infusion device analyzers (IDA) and insulin pumps. The results allowed the manufactures and end users to understand better the behavior of the devices after installation and use.



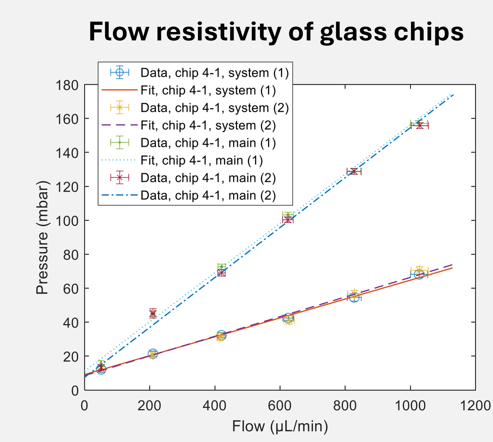


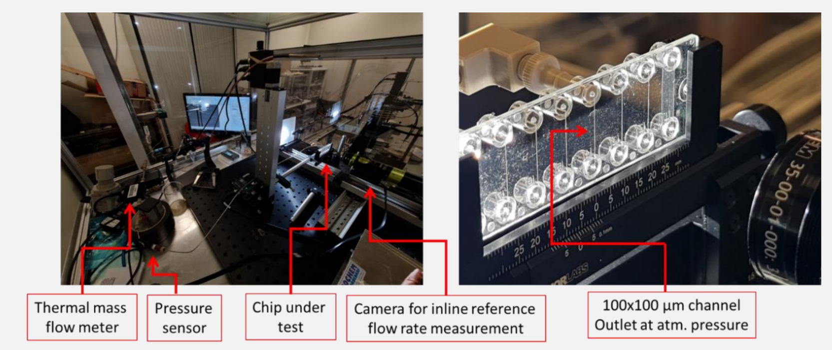




Results and research activities in microfluidics

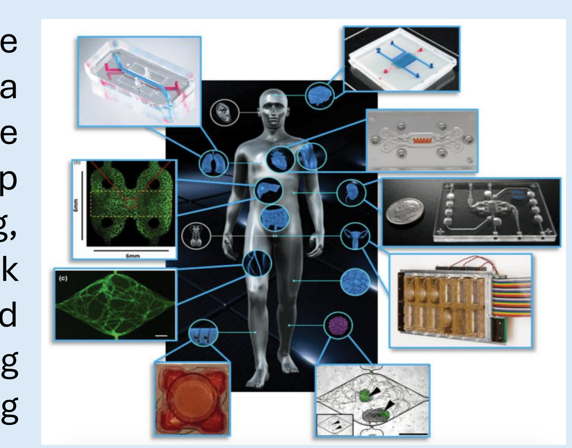
The development of the new flow facilities has also allowed flow measurements to be extended to another field – microfluidics. EMPIR Project MFMET – Establishing standards in microfluidic devices started in 2021. This project investigated the measurement methods of several quantities such as flow resistivity, leakage, surface roughness and liquid properties, among others in different chips (made of glass and TOPAS) specially designed and manufactured in the project and led to the publication of a new EURAMET Technical Guide 4 - Evaluation of flow related quantities in microfluidic devices.





Future developments

Advances in microfluidics and nanotechnology have enabled portable mini-labs, yet standardized performance assessment remains a challenge. While harmonization efforts have begun, regulations are still needed to qualify entire microfluidic systems. In Organ-on-a-Chip (OoC), progress is driven by the need to replace animal testing, backed by the FDA Modernization Act 2.0. However, companies lack standard methods for validating manufacturing, performance, and safety. The EPM MFMET II project aims to fill these gaps by developing protocols and guidelines to support standardization efforts, including ISO/TC 48/WG 3.



Conclusions

Metrology is a key enabler of innovation and patient safety in healthcare. By ensuring the accuracy and reliability of drug delivery systems and diagnostic devices, like organ-on-chips, metrology helps reduce errors, enhance treatment efficacy, and save lives.

Going forward, standardized calibration methods, advanced measurement techniques, and collaborative research will be essential in shaping the future of healthcare technology.

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Improving the accuracy of medical devices will reduce dosing errors and saves lives!