FINAL PUBLISHABLE REPORT

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Project short name	MeDDII
Project full title	Metrology for drug delivery

Project start date and duration:		01 June 2019, 42 months
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Internal Funded Partners: 1. IPQ, Portugal 2. CETIAT, France 3. CMI, Czechia 4. DTI, Denmark 5. METAS, Switzerland 6. NEL, United Kingdom 7. NQIS, Greece (withdrawn from 24 February 2022) 8. RISE, Sweden	External Funded Partners: 9. DNV, Netherlands 10. HSG-IMIT, Germany 11. INESC MN, Portugal 12. THL, Germany 13. UMCU, Netherlands 14. STRATH, United Kingdom (joined from 3 October 2019)	Unfunded Partners: 15. BHT, Netherlands 16. KRISS, Republic of Korea
RMG: -		

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1 Overview

The overall aim of this project was to improve dosing accuracy and to enable the traceable measurement of volume, flow and pressure in existing drug delivery devices and in-line sensors operating at very low flow rates, down to 5 nL/min. This was achieved through the development of new calibration methods and by expanding the existing metrological infrastructure. This project also investigated fast changing flow rates, which are step changes between two flow rates within a second, the physical properties of mixtures of liquids and occlusion phenomena in multi-infusion systems in order to prevent inaccurate measurement results and consequently this improved patient safety.

In general, the project supported the development of standards incorporating robust calibration procedures, equipment, and conditions, which were capable of supporting accurate drug delivery results and reduced risks of adverse patient incidents. Several partners published new CMCs following updates to their facilities and they have already performed several calibrations of drug delivery devices for customers. Also, several workshops for end users, scientists and metrologist were performed with very good feedback from all of the attendees.

2 Need

The most commonly used form of therapy in health care is infusion therapy, which implies that drug delivery is an important topic in this sector. Due to its widespread application in critical health care, the infusion errors can often result in dramatic effects especially in neonatology. There was therefore an urging need to prevent these adverse incidents, morbidity and mortality, which were often traced back to poor inaccurate dosing.

With that in mind, EMRP JRP HLT07 MeDD found that drug delivery devices play a critical role in the safety of patients and a review was published which reported the medical errors associated with flow rate variability in drug delivery devices. One important conclusion from that study was that these errors may result in serious health consequences for the patient including severe health problems or death.

Patient monitoring gives an indication of possible dosing errors, which usually results in an adjustment of the flow rate. However, in multi-infusion applications the actual dosing conditions beyond the mixing point in the infusion line were not known and might therefore deviate from the intended dose. Hence, the accuracy of flow rate set point adjustments based on the patient's vital signs is insufficient to ensure the safe delivery of drugs. To mitigate this problem, a well-defined metrological infrastructure was needed to allow drug delivery device manufacturers to get reliable information on the actual dose at the point of entry in the patient. These efforts enabled users to have better metrological knowledge of the devices, preventing incorrect measurement results. Ultimately this resulted in a significant improvement of patient safety and in a significant reduction of morbidity and mortality.

Metrology is a powerful science to bridge the existing knowledge gap in this area. In EMPIR JRP 18HLT08 MeDDII one of the goals to support it, was based on the design of a representative multi-infusion system to test how different liquids mix and how this affected the drug concentration. The goals of this project already foresaw the increasing implementations of novel microfluidic solutions in healthcare, which required the development of a metrological infrastructure for validating quality and reproducibility.

3 Objectives

The overall objective of this project was to enable traceable measurements of the volume, flow rate and pressure of existing drug delivery devices (and other medical devices, like infusion pump analysers and organ-on-a-chip) and in-line sensors that work at a flow rate lower than 100 nL/min. This project also investigated fast changing flow rates, liquid mixing behaviour and occlusion phenomena in multi-infusion systems in order to improve the dosing accuracy in each infusion line.

The specific objectives of the project were:

1. To develop new traceable techniques for generating and measuring the response or delay time of drug delivery devices regarding changes in flow rate, from 5 nL/min to 100 nL/min, using Newtonian liquids (WP1). For steady flow rates an uncertainty of 1 % (k=2) or better is expected, whereas for

fast changing flow rates an uncertainty of 2 % (*k*=2) or better is expected. The techniques developed will be used to characterise and validate the different response times of at least 3 different types of drug delivery devices (including infusion analysers) (WP3 and WP4) and one type of flow sensor, to accurately measure the administered flow and volume with the required uncertainties.

2. To upgrade the existing flow facilities and knowledge of the partner NMIs in order to enable the traceable in-line measurement of the dynamic viscosity of Newtonian liquids, as a function of the flow rate and pressure difference, with a target uncertainty value of 2 % (*k*=2). The measurement uncertainty will be validated using Newtonian liquids with traceable dynamic viscosity calibration. Additionally, tests with non-Newtonian liquids will be performed in order to prove the concept. To calibrate transfer standards for the in-line measurement of dynamic viscosity and other physical properties of liquids, in order to use these transfer standards for flow measurement and to determine the mixing behaviour of different liquids.
3. To develop and validate novel calibration procedures for existing medical flow devices (e.g. infusion pumps, pain controllers and infusion pump analysers) with traceability to a primary standard and with a target uncertainty value of 2 % (*k*=2) for a range of 5 nL/min up to 600 ml/min and also to develop a proof-of-concept on-chip microfluidic pump used as a transfer standard in drug discovery and organ-on-a-chip applications for flow rates lower than 100 nL/min.
4. To design and develop a multi-infusion system containing check valves, with several options for testing how liquids, with different viscosities mix and flow and how this affects drug concentration. The flow rates and pressures will be traceably calibrated in all infusion lines, as well as at the outlet of the syringe pump, to be able to analyse the effects of pressure-equalising devices and to detect occlusion phenomena and bad mixing configurations.
5. To facilitate the take up of the technology and measurement infrastructure developed in the project by the measurement supply chain (i.e. accredited laboratories, instrumentation manufacturers, etc.), standards developing organisations (ISO/TC 30, ISO/TC 48, ISO/TC/SC 62D, ISO/TC 69, ISO/TC 76, ISO/TC 84, ISO/TC 150, ISO/TC 210) and end-users (i.e. hospitals and health centres).

4 Results

4.1 Objective 1: To develop new traceable techniques for generating and measuring the response or delay time of drug delivery devices regarding changes in flow rate, from 5 nL/min to 100 nL/min, using Newtonian liquids. For steady flow rates an uncertainty of 1 % (k=2) or better is expected, whereas for fast changing flow rates an uncertainty of 2 % (k=2) or better is expected. The techniques developed will be used to characterise and validate the different response times of at least 3 different types of drug delivery devices (including infusion analysers) and one type of flow sensor, to accurately measure the administered flow and volume with the required uncertainties.

One of the key aims of this project was to develop new traceable techniques for generating and measuring the response time to changes in flow rate, in the range from 5 nL/min to 100 nL/min, using Newtonian liquids. The project partners (IPQ, CETIAT, METAS, RISE, CMI; DTI, HSG-MIT, BHT, THL, STRATH(UoS), NEL) developed new techniques to characterise and validate the response times of the different types of drug delivery devices. New innovative approaches were developed, including PIV and optical methods.

The approaches used for the primary reference and the flow generator differ between the laboratories with options for the primary reference including gravimetric systems, interferometry, and various optical tracking systems including particle and optical interface tracking. The different laboratories are described in detail below[1] [2].

[1] Deliverable D1: A1.2.5 Calibration methods for measuring the response or delay time of drug delivery devices using Newtonian liquids for flow rates from 5 nL/min to 100 nL/min.

[2] C. Mills et al. Calibration methods for flow rates down to 5 nL/min and validation methodology. Biomed. Eng.-Biomed. Tech. 2022. https://doi.org/10.1515/bmt-2022-0049

Table 1. Summary of the characteristics of each participating flow laboratory

	Primary reference	Flow generator	Flow rate range	Uncertainty (k=2)[b]	Temperature	Pressure
IPQ	Interferometry	Syringe pump	5 nL/min to 2000 nL/min	2.7 % to 1.3 %	Ambient	Atmospheric
CETIAT	Optical interface tracking	Syringe pump	1 nL/min to 16667 nL/min	11 % to 0.15 %	10°C to 50°C	0 to 2.5 bar
METAS	1. Gravimetric (dynamic) 2. Piston prover[a]	Piston prover	20 nL/min to 400000000 nL/min	1 % to 0.07 %	Ambient	0 to 10 bar
RISE	Gravimetric (dynamic)	Syringe pump	5 nL/min to 16667 nL/min	5 % to 0.5 %	Ambient	0 to 5 bar
DTI	Gravimetric (dynamic)	Syringe pump	0.283 nL/min to 166667 nL/min	5 % to 0.5 %	Ambient	Atmospheric
HSG-IMIT	Particle Tracking Velocimetry (PTV)	Syringe pump	70 nL/min to 1500 nL/min	13.7 % to 0.8 %	Ambient	Atmospheric
BHT	Gravimetric (dynamic)	Pressurised vessel	5 nL/min to 33000 nL/min	29.2 % to 0.25 %	Ambient	1 bar to 9 bar
THL	Optical interface tracking	Syringe pump	50 nL/min and 500000 nL/min	4 %	Ambient	1 bar to 6 bar
UoS/NEL	Particle Tracking Velocimetry (PTV)	Syringe pump	5 nL/min to 100 nL/min	21 % to 5.5 %	Ambient	Atmospheric

[a]METAS have two traceable primary standards to cover micro-flows and nano-flows
[b]The uncertainty values have been inverted with respect to the flow rate range

Interferometry

Instituto Português da Qualidade (IPQ) utilised interferometry as the primary reference for their nano-flow measurements. The IPQ primary system comprised the following components: a laser unit (A) with a detector incorporated (an optical arrangement composed of two retroreflector cubes (C) (one of which had a beam splitter attached (B)), Control Unit, pusher block, syringe pump Nexus 3000 (D) with removable glass syringe (E), (Figure 1). The flow was generated via a stepper motor which drove a screw connected to a pusher block that itself pushed the syringe piston.

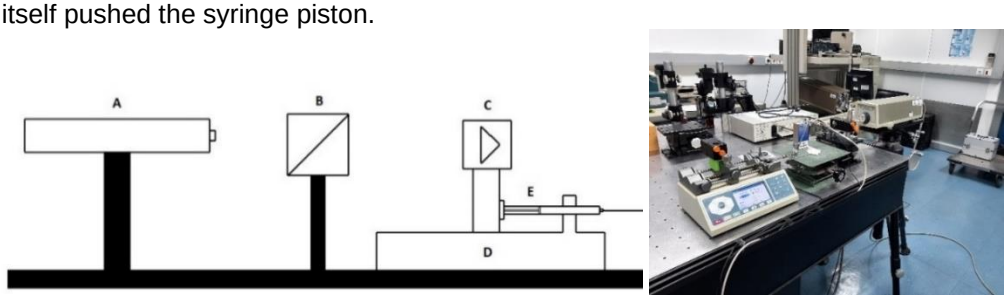


Figure 1. Assembly of the interferometric method setup at IPQ

The IPQ laser interferometry method measured the intensity of a wave resulting from the overlapping of two or more waves that have travelled over different distances and are superimposed on a single point therefore this methodology can be applied to measure the distance of the pusher block of a flow generator connected to a glass syringe to determine the flow rate. The flowrate can be determined with the following equation:

$$Q = v \times A = \frac{x_2 - x_1}{\Delta t} \times \pi r^2 = \frac{d\pi r^2}{t} \quad (1)$$

where Q is flowrate, v is velocity, A is area, x are the start and end distance, Δt is the measured time, r is the syringe radius, and d is the distance.

The main standard uncertainties considered were distance (d), time (t), radius of the syringe (r), stability of the setup (δQ_{sta}), water temperature (T), time (t), expansion coefficient (γ), standard deviation of the measurements (δQ_{rep}) and repeatability of the 3 repetitions. The expanded uncertainty ranged from 2 % (k=2)

to 3 % (*k*=2) in the comparison performed, but during the project, and the tests performed by Elsa Batista in her PhD, it was possible to go down to 1.6 nL/min with a 1.9 % uncertainty[3].

Optical tracking systems

At Centre Technique des Industries Aérauliques et Thermiques (CETIAT), the facility consisted of a JAI SP-12000M-CXP4-F camera (188 fps at 12 MP), Qioptiq Optem FUSION Lens System 7:1 with a motorised zoom controller and a KL 2500 LED backlight for image acquisition, Quartz glass capillaries with inner diameters ranging from 250 µm to 1 mm to circulate water or water and oil, and 4 translation and 1 rotary stage (Figure 2).

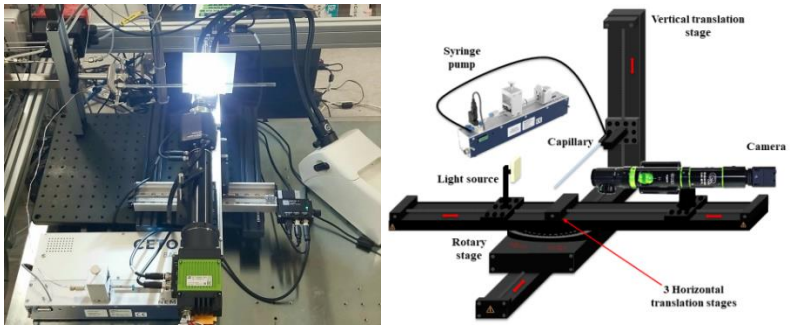


Figure 2. Interface tracking measurement method setup at CETIAT

The camera calibration was completed using a calibrated Olympus OB-M transmitted light objective micrometer. A signal generator that had been calibrated against an atomic clock was used for triggering the camera to start image acquisition. Liquid flow was generated by a CETONI Nemesys syringe pump (using 1 mL to 10 µL syringes) [4]. The relative expanded (*k* = 2) uncertainty was between 11 % and 0.15 % from 1 nL/min to 16 µL/min.

The Technische Hochschule Lübeck (THL) facility incorporated high precision capillaries (0.15 mm to 1 mm inner diameter) in combination with telecentric lenses and a high-speed camera to examine flows between 50 nL/min and 500 µL/min at sample rates up to 5 kHz (5000 fps). Acquisition times between 2 s and 60 s were possible. The acquisition time (between 2 s and 60 s) and resolution could be adjusted via different capillary diameters (150 µm, 300 µm, 600µm, 1000µm), different magnifications (2x, 4x, 5x) of the measuring lenses and via the recording speed. The camera was mounted on a linear stage to adjust the distance after a lens change. The capillary was mounted with an adjustable holder on a linear stage (Figure 3).

The inner diameters of the capillaries were determined with a Keyence digital microscope VHX600. The conversion factor (pixel to µm) was determined with a glass scale from Leica. The expanded uncertainty was 4 % (*k*=2) for flow rates higher than 50 nL/min.

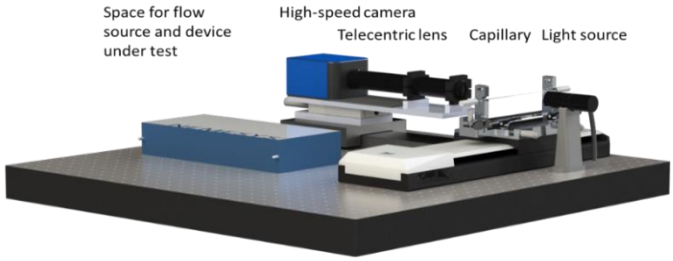


Figure 3. Camera-Front-Tracking-System at Technische Hochschule Lübeck

Hahn-Schickard (HSG-IMIT) developed a test stand for measuring small flow rates (70 – 1500) nL/min based on Particle Tracking Velocimetry (PTV) or Particle Image Velocimetry (PIV).

[3] Elsa Batista, Isabel Godinho, Rui F. Martins, Ricardo Mendes, João Robarts, Development of an experimental setup for microflow measurement using interferometry, Flow Measurement and Instrumentation, Volume 75, 2020

[4] Ogheard F, Cassette P, Boudaoud A. Development of an optical measurement method for “sampled” micro-volumes and nanoflow rates. Flow Meas Instrum 2020;73:21–32.

HSG-IMIT used the optical measurement technique, Micro-PTV, for flow velocity determination. The method measures the displacement of tracer particles between two points in time. The experimental set-up of a PTV system consisted of several subsystems: a transparent micro channel with seeded tracer particles, a light source, a camera to record a sequence of frames and software to determine the flow velocity.

A non-contact optical method was used for determining velocity fields in fluid mechanics. Particles (1 – 10) µm in the fluid were imaged at short time intervals through a holography setup. The direction and speed of movement could be determined from the particle positions. The holographic lens-free setup had the advantage that no errors due to magnifications were included in the measurement and thus the uncertainty budget could be reduced. The uncertainty of the HSG-IMIT facility varied with respect to the flow range from approximately 13.7 % (k=2) at 70 nL/min up to 0.8 % (k=2) at 1500 nL/min, where the progression is approximately exponential.

The University of Strathclyde / TÜV SÜD National Engineering Laboratory nano-flow facility comprised five components: microfluidic chip, pressure system, fluorescent microscope, charged-coupled device (CCD) camera, and software interface.

Fluids with a known concentration of fluorescent beads (1 µm diameter) were introduced into the microfluidic chip from a fluid reservoir under adjustable positive pressure (ranging from 50 mbar to 200 mbar). The geometry of the microfluidic channel in the chip determined the resulting flow rate according to the pressure value applied. A fluorescent microscope was used to illuminate the flow behaviour inside the chip. A camera (1 Hz to 500 Hz acquisition rates) was used to record images of beads moving in the flow using a LabView interface. An in house developed software routine (Matlab) was then used to calculate the velocity of the beads and to extrapolate the flow rate according to the geometry of the microfluidic channel used. The overall uncertainty of the flow rate measurement was calculated based on the variation in dimension of the microfluidic channel and the uncertainty of the position of the bead in each frame depending on the frame rate used. These expanded uncertainty values were in the region of 5.5 % (k=2) to 21 % (k=2) depending upon the flowrate.

Gravimetric

The Eidgenössisches Institut für Metrologie METAS (METAS) facility had two different traceable primary standards available depending on the flow rate. The Microflow and Milliflow facilities incorporated homemade piston provers for the generation of flow and as a primary flowrate reference. METAS also had a dynamic gravimetric reference system that consisted of filling the measurement beaker with the test fluid and continuously measuring the mass with respect to time with an acquisition rate of 10 Hz. Several corrections were applied for sources including evaporation and buoyancy correction. The ambient conditions were well controlled and recorded to avoid any temperature instabilities in the absolute temperature and temperature gradients.

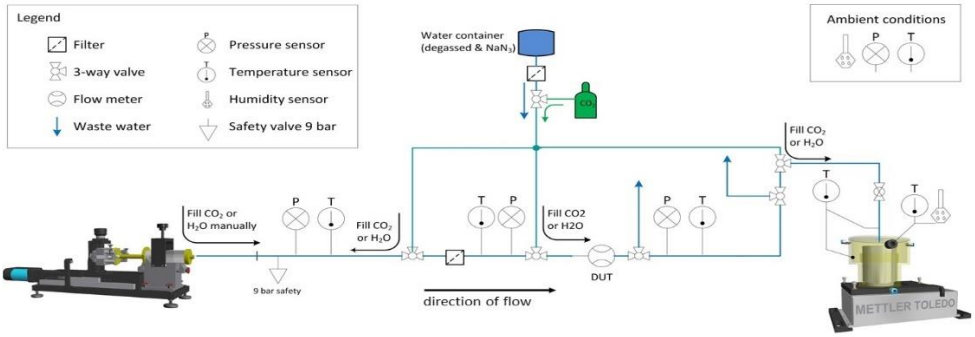


Figure 4. Schematic of the gravimetric method setup at METAS

Whilst not a gravimetric system, the piston prover has been included in this sub-section. The piston prover in METAS's Microflow facility had a speed range from 0.1 mm/s to 0.1 µm/s. The real time position of the prover piston was used to calculate the real time speed by means of linear least square fit over an adjustable time window. Multiplying the speed with the cross section of the piston produced the reference volumetric flow rate.

For static calibrations in the range 20 nL/min to 400 mL/min the relative expanded measurement uncertainty varied from 1.0 % (k=2) to 0.07 % (k=2). METAS also have the capability to measure dynamic flow with the piston prover and the gravimetric system. The relative expanded measurement uncertainty varied from 2.0 % (k=2) to 0.2 % (k=2).

The RISE Research Institutes of Sweden AB (RISE) flow facility for the measurement of ultra-low liquid flowrates and quantities also utilised a gravimetric primary reference. The flow was generated by means of a high-precision CETONI Nemesys syringe pump. The device had calibrated glass and stainless-steel syringes with traceable volumes ranging from 10 µL to 100 mL. The facility is situated in a temperature-controlled laboratory. The measuring conditions in the laboratory (air pressure, room temperature and humidity) are measured and recorded separately. After the measurements, several corrections for evaporation and buoyancy effects were applied. For static calibrations, the relative expanded measurement uncertainty varied from 5.0 % (k=2) (5 nL/min) to 0.5 % (k=2).

The facility can also be operated under dynamic conditions (rapid flow changes). The quantification of the rapid flow changes mainly depends upon the read-out of the weighing scale. In general, the weighing scale was recorded at a higher frequency of about 10 Hz to successfully capture rapid changes. The relative expanded measurement uncertainty for dynamic measurements varied from 5.0 % (k=2) (20 nL/min) to 0.5 % (k=2).

The Cesky Metrologicky Institut (CMI) developed a special beaker eliminating systematic errors due to changing buoyancy and capillary forces when used in the gravimetric method for micro-flow calibrations.

The Danish Teknologisk Institut (DTI) flow facility had a dynamic gravimetric primary standard that measured the change in mass over time. The mass change, Δm, was based upon the measurements made with a high resolution, fast response weigh scale. The facility was installed on a granite table to ensure there were no vibrations influencing the measurements. A custom-built isolation chamber was also used to reduce environmental factors.

The DTI weigh scale can record data with a frequency of 10 Hz and can be used for measuring both dynamic and transient conditions.

The flow was generated using syringe pumps across the range of 0.283 nL/min to 166667 nL/min with an associated measurement uncertainty of 5.0 % (k=2) to 0.5 % (k=2).

The Bronkhorst (BHT) flow facility had a high precision balance as the primary reference. The facility can be used for static and dynamic measurements. The setup consisted of a pressurised liquid tank, filter, degasser, pressure sensor, control valves, balance, temperature sensors, humidity sensors, and shut-off valves. Like the DTI facility, the BHT facility had been situated on a granite table for stability. It was also housed in an enclosure to reduce temperature fluctuations and with a humidity-controlled environment to reduce humidity variations.

The primary standard at Bronkhorst used a high-precision balance as the mass flow reference. This was implemented by differentiating the measured mass (Δm) to measured time (Δt). The sample time equals 100 ms and the calculated mass flow was filtered using a 60 s moving average.

For static calibrations in the range 5 nL/min to 33000 nL/min the relative expanded measurement uncertainty varied from 29.2 % (k=2) to 0.25 % (k=2). BHT also have the capability to measure dynamic flow with the gravimetric system. The gravimetric balance was read out at a frequency of 10 Hz. The relative expanded measurement uncertainty varied from 163 % (k=2) to 543 % (k=2) in the range of 30 nL/min to 100 nL/min.

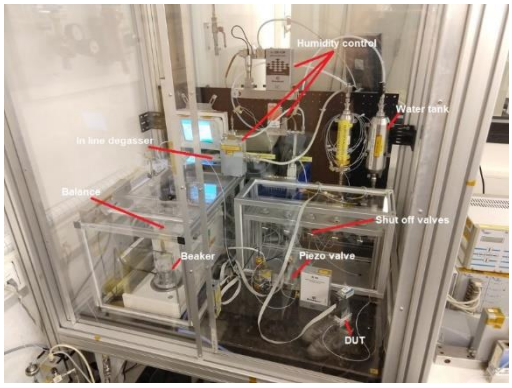


Figure 5. Bronkhorst calibration facility

Validation of primary standards

These new traceability chains and primary standards for ultra-low flow rate facilities were validated with an inter-comparison of nine partner laboratories BHT, IPQ, CETIAT, HSG-MIT, METAS, DTI, THL, UoS/NEL and RISE (Figure 6 – Figure 7)[5]. All the measurement results for this comparison including deviations and uncertainties can be found in the final report of EURAMET project 1508. The validity of the comparison is further enhanced due to the partner laboratories BHT, IPQ, CETIAT, HSG-MIT, METAS, DTI, THL, UoS/NEL and RISE utilising different reference systems based upon separate traceability chains.

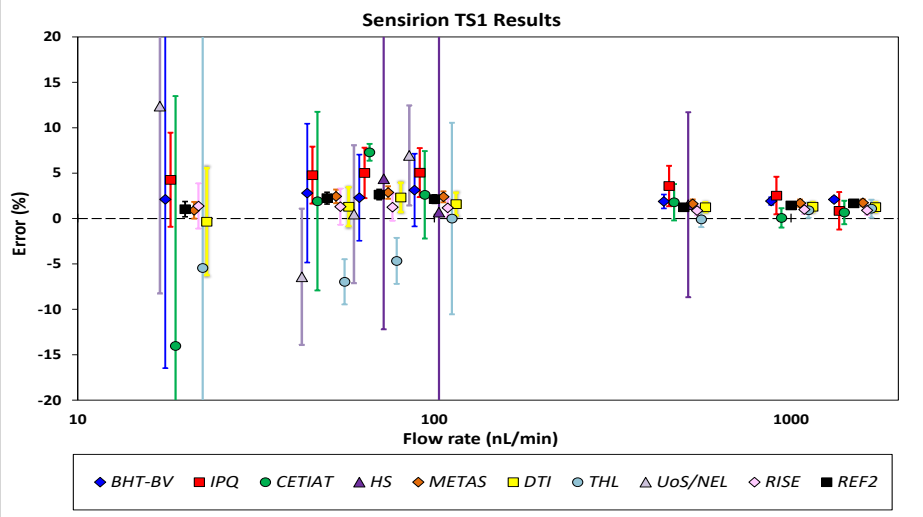


Figure 6. Sensirion flow meter [TS1] top static results

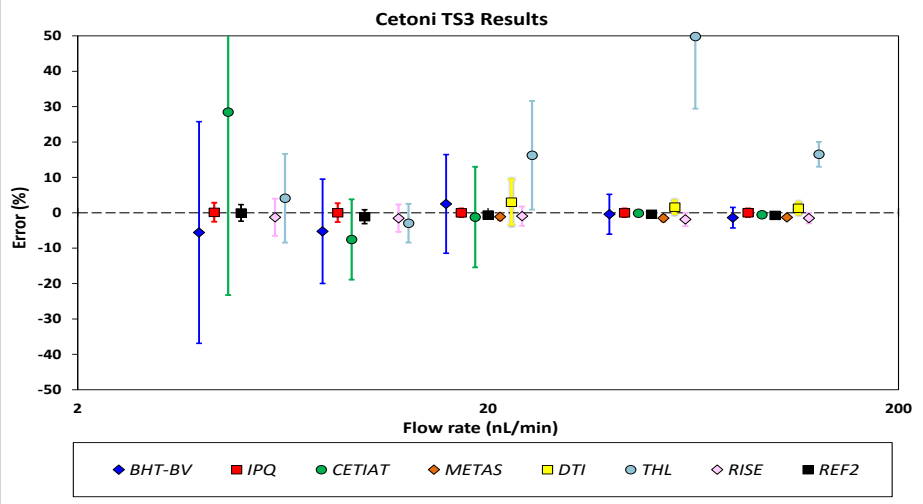


Figure 7. CETONI Syringe pump [TS3] static results

The inter-comparison was deemed to be a success and it enabled the consortium to share knowledge, improve their methodologies, evaluate their measurement uncertainties, and enhance their calibrations facilities. All participants succeeded in performing the evaluation with at least one Transfer Standard at several flow rates and to obtain results in line with the agreed protocol.

Following the completion of the inter-comparison, the project partners IPQ, METAS, RISE and CETIAT successfully published new Calibration and Measurement Capabilities (CMCs) in the BIPM database.

[5] Deliverable D2: A1.3.5 Report on the results from the inter-comparison of the primary standards and improved measurement facilities for flow rates from 5 nL/min to 1500 nL/min (with uncertainty targets of 1 % (k=2) for steady flow and 2 % (k=2) for fast changing flow).

Summary

The partners METAS, IPQ, CETIAT, NEL, THL, HSG-MIT, RISE, DTI, CMI and BHT have developed or upgraded their facilities to cover the flow rate ranges from 5 nL/min to 100 nL/min for static calibrations and BHT, CETIAT and METAS also for dynamic calibrations. These new primary standards for ultra-low flow rate were validated with an inter-comparison, which was extremely successful and enabled the partners to share knowledge, improve their methodologies, evaluate their measurement uncertainties, and enhance their calibrations facilities. The static calibration could be performed for flow rates down to 5 nL/min with an uncertainty of 3 %, which is slightly larger than the targeted uncertainty, but still covers the need of the industry. The dynamic calibration could be validated for flow rates down to 30 nL/min with an uncertainty of 2 %, although the facilities are able to generate dynamic calibrations down to 5 nL/min. However, a suitable transfer standard for these low flow rates is not yet commercially available. Overall, the objective was fully achieved with a slightly larger measurement uncertainty than expected.

4.2 Objective 2: To upgrade the existing flow facilities and knowledge of the partner NMIs in order to enable the traceable in-line measurement of the dynamic viscosity of Newtonian liquids, as a function of the flow rate and pressure difference, with a target uncertainty value of 2 % (k=2). The measurement uncertainty will be validated using Newtonian liquids with traceable dynamic viscosity calibration. Additionally, tests with non-Newtonian liquids will be performed in order to prove the concept. To calibrate transfer standards for the in-line measurement of dynamic viscosity and other physical properties of liquids, in order to use these transfer standards for flow measurement and to determine the mixing behaviour of different liquids.

The primary standards developed by METAS, NEL and RISE for the in-line measurement of the dynamic viscosity of Newtonian liquids are based on the measurement principle of the pipe viscometer, where all the dimensional parameters as well as all sensors for pressure, temperature and flow rate are calibrated to ensure traceability to SI units. The micro pipe viscometers are described in the next sections[6].

Working principle of a micro pipe viscometer

The micro pipe viscometer consists of a flow generator (piston prover) connected to a tube. Appropriate temperature and pressure sensors are installed upstream and downstream of the micro tube, which finally ends in a liquid collecting reservoir as shown in Figure 8.

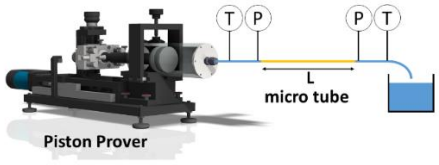


Figure 8: Schematic setup of the micro pipe viscometer with a flow generator (piston prover), temperature and pressure sensors upstream and downstream of the micro tube.

For the laminar flow regime and a straight channel, the Hagen-Poiseuille law describes the relation between the pressure drop, the flow rate, the dynamic viscosity, the length and the inner diameter of the micro tube. This law has been applied to indirectly determine the inner diameter of the micro tube by measuring the pressure drop for a given range of known flow rates with a liquid of known and traceable viscosity. In this case, water was used as the reference liquid. The accurate measurement of the water temperature allows the calculation of the dynamic viscosity according to the NIST database for water properties[7].

[6] Report A2.1.3 "Primary standard for in-line measurement of dynamic viscosity".

[7] Lemmon, E.W., Bell, I.H., Huber, M.L., McLinden, M.O. NIST Standard Reference Database 23: Reference Fluid Thermodynamic and Transport Properties-REFPROP, Version 10.0, National Institute of Standards and Technology, Standard Reference Data Program, Gaithersburg, 2018. https://doi.org/10.18434/T4/1502528

Micro pipe viscometer at METAS

The flow facility at METAS[8] has currently been extended to include a section with a micro pipe viscometer, as can be seen in Figure 9.

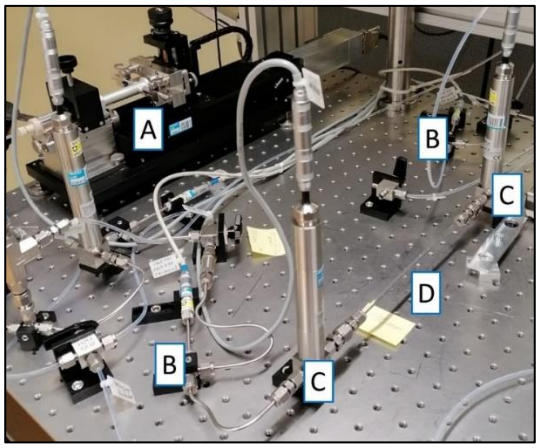


Figure 9: The micro pipe viscometer at METAS: (A) piston prover, (B) temperature sensors, (C) pressure sensors and (D) the glass micro tube with an inner diameter of 0.13 mm and a length of 200 mm.

The pipe viscometer consists of a piston prover to generate the flow and a micro tube with upstream and downstream temperature and pressure sensors. The tubing connected to the pressure sensor and the connectors to the micro tube have much larger diameters (more than 2 mm) than the nominal inner diameter of the micro tubes of 0.13 mm to ensure that the recorded pressure drop between the two pressure sensors is essentially due to the pressure drop over the micro tube. Flow rates from 1 μL/min to 150 mL/min can be generated for the in-line measurement of the dynamic viscosity with a pressure drop up to 10 bar. Glass micro tubes with larger inner diameter are also available, but the measurement results presented here have been obtained with the glass micro tube with the inner diameter of 0.13 mm. The expanded uncertainty $U_{(k=2)}$ of the dynamic viscosity measurement was 0.90 %.

The inner diameter of the glass micro tube is the most challenging measurement for the traceability of the micro pipe viscometer. Therefore, two methods have been applied at METAS to determine this inner diameter: both by means of the μ-CT facility operated at METAS[9] and the flow characterisation method according to the Hagen-Poiseuille law described above. Both methods lead to consistent results within the corresponding measurement uncertainty for the inner diameter of the glass micro tube.

Micro pipe viscometer at RISE

The micro pipe viscometer at RISE consists of a capillary holder and an associated stainless steel micro tube with a nominal inner diameter of 0.18 mm, an outer diameter of 1/16" and a length of 300 mm. The pressure drop is measured by pressure sensors upstream and downstream of the micro tube at pressures up to 5 bar (Figure 10).

[8] Bissig H, Tschannen M, de Huu M (2016) Recent Innovations in the field of traceable calibration of liquid milli-flow rates with liquids other than water. Flomeko 2016, proceedings paper

[9] Bircher B A, Meli F, Küng A and Thalmann R (2020) METAS-CT: Metrological X-ray computed tomography at sub-micrometre precision, euspen's 20th International Conference & Exhibition, Geneva, Switzerland

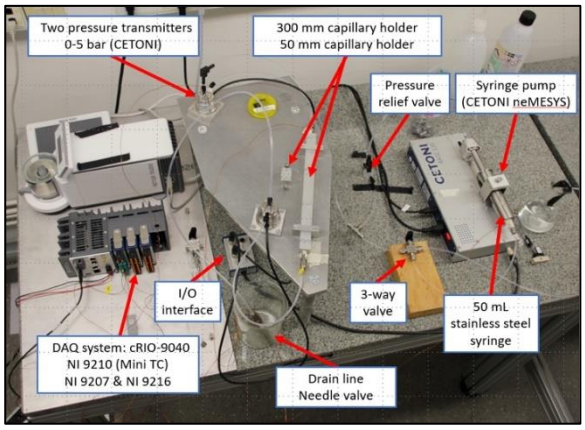


Figure 10: The micro pipe viscometer at RISE with pre-cut stainless steel micro tubes with a length of 50 mm and 300 mm.

The temperature of the test liquid is measured indirectly with two type K thermocouples attached to the inlet and outlet of the capillary holder. The desired flow rate is generated using a syringe pump and calibrated syringes. To account for the pressure loss in all connections, additional measurements have been performed using a micro tube with the same inner diameter but a shorter length of 50 mm. The expanded uncertainty U*(k=2)* of the dynamic viscosity measurement was 2.0% [10].

Micro pipe viscometer at NEL

The micro pipe viscometer at NEL is shown in Figure 11. The calibrated syringe pump generates traceable flow rates and the Coriolis meter provides a secondary flow rate indication, fluid density information as well as the identification of any bubbles or flow disturbances. Two temperature sensors (upstream and downstream sensors) are attached to the outside of the stainless-steel capillaries and used to determine the average fluid temperature. Two calibrated Elveflow pressure sensors (1 bar and 340 mbar) are directly connected to the capillaries to measure the pressure drop. The expanded uncertainty *U(k=2)* of the dynamic viscosity measurement is 1.0 %.

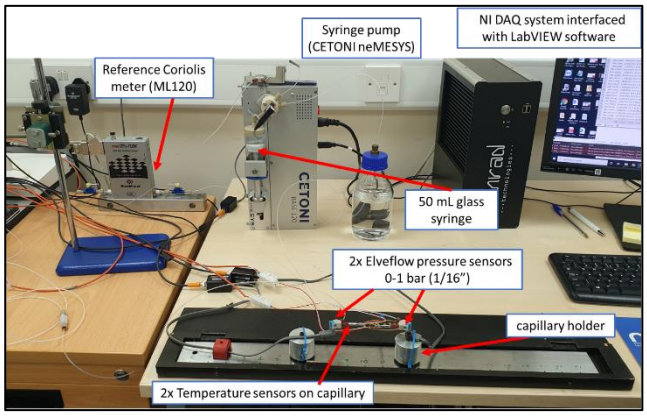


Figure 11: NEL pipe viscometer with a stainless-steel micro-tube with an outer diameter of 1/16 inch (1.6 mm), length of 100 mm and a nominal inner diameter of 180 µm (manufacturer's specification).

Validation of the pipe viscometers by means of measuring the dynamic viscosity of the liquids A – H

To validate the stated uncertainties of the micro pipe viscometers, eight liquids were prepared by IPQ. These liquids cover the clinically relevant range of dynamic viscosity, which has been identified by UMCU, IPQ and METAS. The dynamic viscosity of these liquids has been determined using the newly developed micro pipe

[10] Büker O, Stolt K. RISE Test Facilities for the Measurement of Ultra-Low Flow Rates and Volumes with a Focus on Medical Applications. *Applied Sciences*. 2022; 12(16):8332. https://doi.org/10.3390/app12168332

viscometers and by several other laboratories using their existing instruments or methods[11] [12]. Each laboratory was provided with a 500 mL bottle of each liquid produced in one batch to ensure the same composition in each bottle. In addition, the density of the liquids was also measured, as some instruments measure the kinematic viscosity, which can be converted into the dynamic viscosity with knowledge of the density of the liquid.

The compositions of the eight liquids are listed below:

- **Liquid A**: Saline solution of 0.9 %wt NaCl
- **Liquid B**: Glucose solution 10 %wt
- **Liquid C**: Glucose solution 20 %wt
- **Liquid D**: solution of NaCl 0.22 %wt and Glucose 2.75 %wt
- **Liquid E**: solution of NaCl 0.22 %wt and Glucose 5.55 %wt
- **Liquid F**: solution of NaCl 0.45 %wt and Glucose 5.54 %wt
- **Liquid G**: solution of Glycerol 52.0 %wt
- **Liquid H**: solution of Glycerol 58.8 %wt

The validation of the results of the micro-pipe viscometers is analysed according to the rules of an intercomparison of laboratories, which not only describes the calculation of the reference value, but also defines the consistency check by means of the χ^2-test (chi-squared test)[13]. The chi-squared test is used to check the overall consistency of the set of the results from the laboratories used to calculate the comparison reference value. If the consistency check is passed, all of the results of the laboratories were accepted for the calculation of the reference value. If it failed, the result of the laboratory with the largest contribution χ^2_{obs} is omitted from the calculation of the reference value. Figure 12 shows the results as deviations from the reference values for each laboratory and each liquid, and the error bars indicate the measurement uncertainties. The reference values with their uncertainties are also represented as black diamonds.

The equivalence of the results from each laboratory can be quantified in terms of the normalised equivalent value (*En*), which are listed in Table 2 and details on the calculation and the signification can be found in report A2.1.5[14].

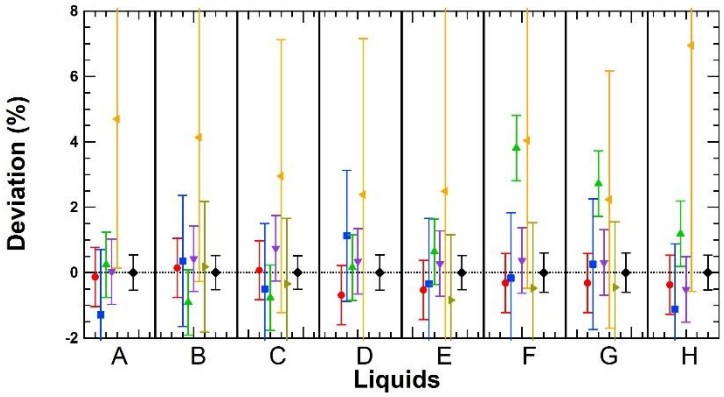


Figure 12: Results for the deviations of the dynamic viscosity measurements performed by the different laboratories compared to the reference value. METAS (red circle), RISE (blue square), NEL (green triangle up), NQIS/EIM (violet triangle down), IPQ (orange triangle left), KRISS (dark yellow triangle right), reference value (black diamond). The deviations of Hahn-Schickard are not shown in the figure as the deviations are larger than the selected range.

[11] Deliverable D3: A2.1.5 "Validation report on the primary standards developed for the in-line measurement of the dynamic viscosity of Newtonian liquids with a target uncertainty of 2 % (*k*=2)".

[12] H. Bissig et al. In-line measurements of the physical and thermodynamic properties of single and multicomponent liquids. Biomed.Eng.-Biomed. Tech. 2022. https://doi.org/10.1515/bmt-2022-0039

[13] Cox M. The Evaluation of Key Comparison Data. Metrologia 2002;39(6):589.

[14] Deliverable D3: A2.1.5 "Validation report on the primary standards developed for the in-line measurement of the dynamic viscosity of Newtonian liquids with a target uncertainty of 2 % (*k*=2)".

Table 2: En-Values for the laboratories that performed the dynamic viscosity measurements. The green values (En < 1) show consistency with the reference values.

	Liquid A	Liquid B	Liquid C	Liquid D	Liquid E	Liquid F	Liquid G	Liquid H
METAS	0.19	0.19	0.09	0.95	0.71	0.48	0.48	0.51
RISE	0.67	0.18	0.26	0.58	0.18	0.09	0.13	0.58
NEL	0.28	1.07	0.90	0.17	0.74	3.29	2.36	1.41
NQIS/EIM	0.03	0.50	0.88	0.42	0.33	0.46	0.39	0.61
IPQ	1.04	0.95	0.71	0.50	0.36	0.90	0.58	0.93
KRISS	n/a	0.09	0.18	n/a	0.43	0.25	0.23	n/a
Hahn-Schickard	0.47	2.39	8.42	3.95	3.03	1.60	11.59	14.91

Pipe viscometer for in-line measurement of dynamic viscosity of non-Newtonian liquids

The dynamic viscosity of two non-Newtonian liquids - Propofol and Gelaspan - was measured by the micro pipe viscometer as a proof of concept for non-Newtonian liquids and compared to flow curves measured by a rheometer. The calculated shear rates and the resulting flow curves are consistent for both methods[15].

Sensor for the in-line measurement of density, dynamic viscosity, pressure and temperature of liquids

Two sensors for in-line measurements of the physical properties of liquids have been investigated[16]. One sensor is the VLO-M1 sensor from TrueDyne Sensors AG[17], which measures the temperature, density, kinematic viscosity and dynamic viscosity of the liquid. The second sensor is the multi-parameter chip sensor from Bronkhorst High-Tech B.V. (technology demonstrator) [18], which measures mass flow, chip inlet and the outlet pressure, density, dynamic viscosity and temperature.

VLO-M1 sensor from TrueDyne Sensors AG (commercially available)

Measurements were performed with the VLO-M1 sensor and the eight liquids A – H, and the results are in excellent agreement with the reference values of density (Table 3) and dynamic viscosity (Table 4) of the eight liquids.

Table 3. Reference value of the density and the results of the VLO-M1 sensor at a temperature of 22 °C. The deviation of the VLO-M1 with respect to the reference value and its measurement uncertainty is also represented in this table.

	Liquid A	Liquid B	Liquid C	Liquid D	Liquid E	Liquid F	Liquid G	Liquid H
Reference value (kg/m^3)	1004.172 ± 0.033	1038.171 ± 0.033	1079.829 ± 0.033	1010.362 ± 0.033	1020.217 ± 0.033	1021.882 ± 0.033	1131.303 ± 0.033	1150.192 ± 0.033
VLO-M1 (kg/m^3)	1004.29 ± 0.20	1038.30 ± 0.20	1079.76 ± 0.20	1010.47 ± 0.20	1020.32 ± 0.20	1021.97 ± 0.20	1131.42 ± 0.20	1150.41 ± 0.20
VLO-M1 Deviation (%)	0.011 ± 0.020	0.012 ± 0.020	-0.006 ± 0.019	0.010 ± 0.020	0.010 ± 0.020	0.009 ± 0.020	0.011 ± 0.018	0.019 ± 0.018

[15] Report A2.1.6 "Measurement of the flow curves (viscosity as a function of shear rate) of two non-Newtonian liquids with the rheometer or rotational viscometer and comparison measurements with the micro-pipe viscometer"

[16] Deliverable D4: A2.3.4 "Report on the use of a calibrated microfluidic multi-parameter chip for the in-line measurement of pressure, viscosity and temperature."

[17] VLO-M1 sensor from TrueDyne Sensors AG, https://www.truedyne.com/viscosity_sensors_for_liquids/vlo-m1-for-liquids/?lang=en

[18] Schut T V P, Alveringh D, Sparreboom W, Groenesteijn J, Wiegerink R J, Lötters J C. Fully integrated mass flow, pressure, density and viscosity sensor for both liquids and gases. MEMS 2018, Belfast, Northern Ireland, UK, January 21-25, 2018

Table 4. The reference values (Report A2.1.4) and the results of the VLO-M1 sensor for the measurement of the dynamic viscosity of the eight liquids at a temperature of 22 °C. The deviation of the VLO-M1 with respect to the reference value including the measurement uncertainty is also represented in this table.

	Liquid A	Liquid B	Liquid C	Liquid D	Liquid E	Liquid F	Liquid G	Liquid H
Reference value (mPa·s)	0.972 ± 0.005	1.274 ± 0.007	1.809 ± 0.009	1.045 ± 0.006	1.116 ± 0.006	1.115 ± 0.007	6.310 ± 0.038	9.453 ± 0.051
VLO-M1 (mPa·s)	0.945 ± 0.047	1.239 ± 0.062	1.740 ± 0.087	1.013 ± 0.050	1.077 ± 0.054	1.080 ± 0.054	6.15 ± 0.31	9.44 ± 0.47
VLO-M1 Deviation (%)	-2.8 ± 5.0	-2.8 ± 5.0	-3.8 ± 5.0	-3.0 ± 5.0	-3.5 ± 5.0	-3.1 ± 5.0	-2.5 ± 5.0	-0.2 ± 5.0

Multi-parameter chip sensor from Bronkhorst High-Tech B.V. (technology demonstrator)

As the reference density values of the eight liquids A – H are known for the temperature range between 20 °C and 30 °C [19], the actual temperature measured by the multi-parameter chip was used to calculate the reference density at the actual measurement temperature, which was at 32.9 °C. The results are listed in Table 5.

Table 5. Reference value of the density extrapolated to the temperature of 32.9 °C according to the temperature dependence reported in Report A2.1.2 (measured by the laboratory IPQ) and the results of the Multiparameter Measurement System (MMS). The results presented are the values including the expanded measurement uncertainty U(k=2). The deviation of the MMS with respect to the reference value and its measurement uncertainty is also represented in this table.

	Liquid A	Liquid B	Liquid E	Liquid F
Reference value (kg/m^3)	1001.06 ± 0.05	1034.67 ± 0.05	1016.94 ± 0.05	1018.57 ± 0.05
MMS (kg/m^3)	996.9 ± 5.0	1025.8 ± 5.0	1012.2 ± 5.0	1012.9 ± 5.0
MMS Deviation (%)	-0.42 ± 0.50	-0.85 ± 0.50	-0.46 ± 0.50	-0.55 ± 0.50

The deviations of the density measurements from the calculated reference values are less than 1 %, which corresponds to the estimated measurement uncertainty of the actual setup of the technology demonstrator. Further developments of the technology demonstrator aim at an uncertainty of 0.5 % for the density measurement. Therefore, the uncertainty of 0.5 % is given in Table 5.

Summary

The micro-pipe viscometers developed by RISE, NEL and METAS for traceable measurement of the dynamic viscosity of Newtonian liquids have been validated by measuring the dynamic viscosity of eight liquids. The results are consistent with facilities or instruments using the well-established capillary glass viscometer method for the measurement of the kinematic viscosity (IPQ, NQIS/EIM, KRISS). The validated uncertainties of the micro-pipe viscometers from METAS, RISE respectively NEL are 0.9 %, 2.0 % respectively 1.0 % and thus fulfil the target uncertainty of 2.0 %.
The dynamic viscosity of two non-Newtonian liquids - Propofol and Gelaspan - was measured by the micro pipe viscometer as a proof of concept for non-Newtonian liquids and the results are consistent with the flow curves measured by a rheometer.
The micro-pipe viscometers are used to calibrate inline sensors for the measurement of dynamic viscosity, which in most cases should have an accuracy of 5 %. The commercially available sensor VLO-M1 from

[19] Report A2.1.2: Newtonian reference liquids and their mixtures: determine liquid properties.

TrueDyne Sensors AG and the technology demonstrators MMS (multi-parameter measurement system) and the conventional VMS (viscosity measurement system) from Bronkhorst High-Tech BV were calibrated with these liquids to verify the accuracy for the measurement of the dynamic viscosity and density.
Overall, the objective was fully achieved.

4.3 Objective 3: To develop and validate novel calibration procedures for existing medical flow devices (e.g. infusion pumps, pain controllers and infusion pump analysers) with traceability to a primary standard and with a target uncertainty value of 2 % (k=2) for a range of 5 nL/min up to 600 ml/min and also to develop a proof-of-concept on-chip microfluidic pump used as a transfer standard in drug discovery and organ-on-a-chip applications for flow rates lower than 100 nL/min.

The aim of this work package is to develop calibration methods and procedures for existing drug delivery devices e.g. insulin pumps, pain pumps etc. The aim is also to develop a prototype of a new on-chip pump. Traceable primary standards, based on gravimetric techniques, PIV and optical methods, will be established with uncertainties less than 2 % for a flow rate range of 5 nL/min up to 600 mL/min. The procedures will be used to develop a new EURAMET guideline.

The work package was divided in three tasks. Where the aim of the first and third tasks was to identify the metrology infrastructure for drug delivery devices that is already in place in hospitals, accredited laboratories and commercial companies/manufacturers in DTI, CETIAT, CMI, METAS, THL, IPQ, UMCU, RISE, NEL, INESC MN, HSG-MIT, KRISS and STRATH's countries. This will focus on identifying gaps in metrological calibration procedures, infrastructure, and traceability. Additionally, it will also clarify which types of devices and parameters/characteristics will be tested to make new relevant calibration guidelines. Thus, the aim of the third task was to test and define calibration procedures for the drug delivery devices identified and selected as the first task. Some drug delivery devices such as insulin pumps have a non-continuous flow rate, where the device delivers a specified bolus (single dose) at a given time interval. Therefore, the aim of this task was also to test these characteristics and developed procedures to determine the correct calibration techniques and procedures for this kind of device.

The aim of the second task was to develop and characterise a prototype microfluidic microchip flow pump that can be used as a traceable standard for the calibration of the drug delivery devices used in drug discovery and organ-on-a-chip technology for flow rate ranges from 5 nL/min to 100 nL/min, with a target uncertainty of 2 %. This microchip will be a movable transfer standard that can be used on site.

Metrological infrastructure survey

In order to identify the gaps and needs in the already existing metrological infrastructure a questionnaire was developed and sent to several commercial companies and medical environments. From this questionnaire and with inputs from collaborators and stakeholders, relevant types of drug delivery device and flowrate intervals were identified and selected for further test.

From the manufactures and hospitals the project received the following answers (in summery):

The manufacturers and the technicians at the hospitals have a quality system implemented to calibrate drug delivery devices (DDD) based on the standards:

- ISO 9001:2015 Quality management systems - requirements
- ISO 13485:2016 Medical devices – Quality management systems – Requirements for regulatory purposes

The calibrations of the DDD are performed in most cases by manufacturers internally, where the gravimetric method is applied according to the following standards:

- IEC 60601-2-24:2012 Medical electrical equipment – Part 2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers
- ISO 28620:2020 Medical devices – non-electrically driven portable infusion devices

They guarantee traceability only through the traceable calibration of the balance, but not through the validation of the entire gravimetric method with its measurement uncertainty.

The manufacturer applying the ISO 28620:2020 stated that the calibrations are performed externally.

All manufacturers stated that the calibrations of the DDD are performed to verify if the performance is within

the specifications, to ensure traceability of the measurement and to satisfy the requirements of their quality management system.

The calibrations are performed either externally or internally. If the calibrations are done externally, the DDD are often sent to the manufacturer to perform the calibration. If the calibration is done internally, the following methods are applied:

- Gravimetric method according to IEC 60601-2-24:2012 Medical electrical equipment – Part 2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers.
- Infusion Device Analyser (IDA), which are sent for calibration to the manufacturer or an accredited laboratory for flow and pressure measurements.

The meaning of traceable calibration of the flow rate measurement seems not to be a familiar expression. One of the technicians of the hospitals writes that the calibration is done according to IEC 60601-2-24 with the gravimetric method. For this case, they are probably convinced that following a standard method means that the calibration is traceable with a calibrated balance. The other technician of the hospital explicitly states that traceability is not guaranteed and that the IDA was sent to a NMI for calibration once five years ago for validation of their internal calibration. He states that calibrations are mainly used for verification of the performance of the IDA.

The technicians of the hospitals stated that for medical electrical equipment after repair the following standard IEC 62353:2014[20] was used.

The nurses, the user, and the anaesthesiologist state the same answers as the clinical technician whenever they answered the questions.

Based on the outputs from the questionnaire three DDD were selected for the test and characterisation. Along with the three devices the infusion device analyser was also selected. It is often used to test the syringe pumps at the hospital maintenance departments. The four devices were an infusion device analyser, a syringe pump, an insulin pump, and an implantable pain control pump.

Also based on the inputs it was stated that the typical clinically relevant flow rate ranges are within 1.0 µL/min to 10.0 mL/min.

From the questionnaire the typical drugs used in clinical settings were identified and based on these inputs. The following drugs were selected for test with the syringe pump; Dobutamine, Dopamine, Propofol, Gelaspan, and saline solution.

For the four selected devices test protocols and calibration procedures were developed and a measurement campaign arranged, where the four devices were circulated among DTI, THL, METAS, RISE, STRATH, NEL, IPQ, CMI and KRISS to be tested in their laboratories. Due to malfunction, the implantable pain pump was excluded from the measuring campaign; however, measurements were made for the remaining three devices and the results were analysed and discussed. All the processed data were collected in an available report[21].

Infusion device analyser (IDA):

Infusion device analysers are used to verify the accuracy of the drug delivery devices by the users or maintenance officers in the hospitals. These devices are normally calibrated by the manufacturer before they are sold. Then, subsequently, in many cases, calibrations are not considered and there are no available documents that explain how this should be performed. Therefore, it is very important to define the calibration procedures that are in use for this type of equipment.

[20] IEC 62353:2014 Medical electrical equipment – Recurrent test and test after repair of medical electrical equipment

[21] ”A.3.3.1 - Characterization of flow rate, volume, type of liquid, bolus and other related characteristics of an insulin pump, a syringe pump, a pain pump and a Infusion device analyser”, available from www.drugmetrology.com.

In Figure 13 the calibration result of the 6 laboratories, who have tested the IDA, can be appreciated. The calibration results obtained by the 6 laboratories are all consistent but show larger deviations at lower flowrates than in the higher flowrate ranges. This is possibly due to a combination of a higher uncertainty of the calibration facilities and the IDA itself. Increasing the acquisition time will lead to a smaller uncertainty because the standard deviation of the IDA is one of the largest uncertainty components.

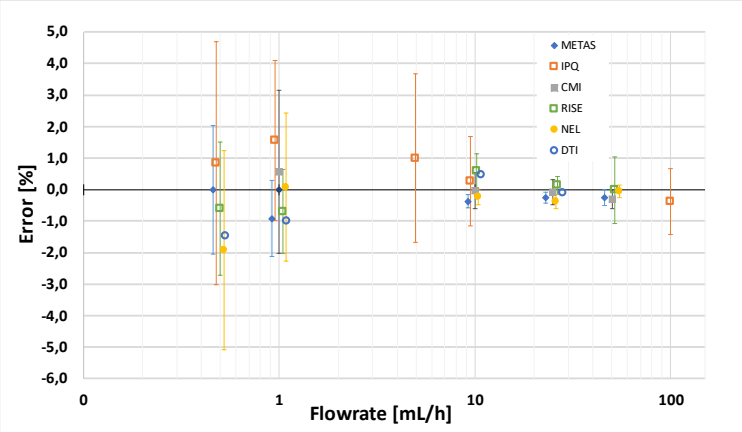


Figure 13: IDA flow error determination with water

The manufactures recommend tests with a delivered volume of 10 ml or 20 ml depending on the flow rates tested. At very low flow rates this represents many hours of measurements which may not be feasible for a calibration laboratory. Tests were performed at different flow rates using different delivery volumes (acquisition times). It can be shown that at measurement volumes of 2 mL or 3 mL the deviation (error) of the IDA is already stable for all flow rates. This means that the measurement duration can be shorter than recommended by the manufacturer.

The IDA is an instrument mainly used by hospitals to verify the performance of syringe pumps and peristaltic pumps. The traceability of this instrument is still a problem for most users due to the lack of information on subsequent calibration procedures in most European countries. The main objective of this work was to provide some relevant information about the use and performance of an IDA. Several tests were carried out: flow error determination, use of different calibration liquids, different acquisition times (volumes), reproducibility, use of different calibration methods and a detailed description of the uncertainty components. The instrument was found to be repeatable and reproducible in flow measurements. It is possible to reduce the measuring time without compromising the accuracy of the measurements, the IDA is not affected by the properties of the calibration liquid, the use of a reference syringe pump method is recommended. The uncertainty values and errors obtained are within the accuracy of the IDA, even at lower flow rates where the largest errors were found.

Calibration of the IDA at an accredited laboratory will ensure the traceability to a commonly agreed standard/procedure. Basically, for flow rates it is mass and time. This traceability is transferred to the infusion device e.g., a syringe pump, when it is calibrated with the IDA as the reference. This is called the metrological infrastructure and ensures that the devices used in a clinical environment operate within a documented error and uncertainty. In some cases, the uncertainty can be higher e.g., general adult anaesthetics, than in other cases, e.g., treatment of premature infants. However, despite the intended use of the infusion device, it is always important to know the level of uncertainty.

Syringe pump

Syringe pumps are widely used in hospitals to administer small amounts of fluids or drugs to patients. The calibration procedure for manufacturers is well defined in IEC 60601-2-24[22] but the calibration procedure during use is not defined in any documentation. Also, the accuracy of these devices at very low flow rates (e.g. 0.1 mL/h) were not thoroughly investigated.

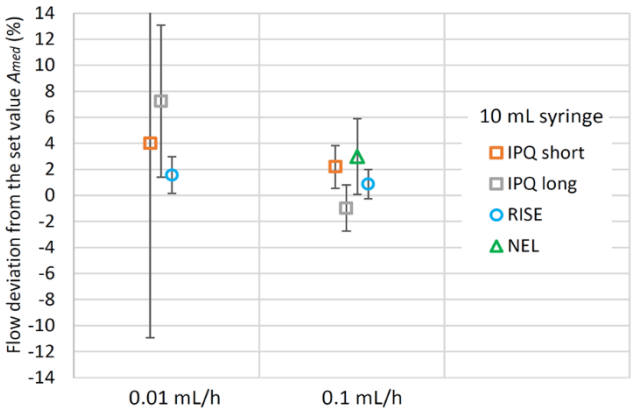


Figure 14 Comparison of calibration results for the average flow rate obtained in various labs. The bars represent the expanded uncertainty of the resulting flow rate deviation.

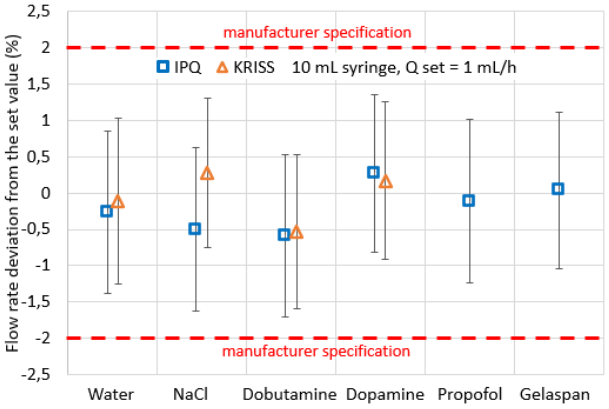


Figure 15 Flow rate deviation from the "set value" for a syringe pump using different liquids

Extremely low flow rates of 0.01 mL/h and 0.1 mL/h have been tested with the 10 mL syringe approaching the lower flow rate limit of the syringe pump according to the manufacturer's specifications. The percentage deviation of the average flow rate from the set point value calculated, including the error bars representing the expanded uncertainties at the confidence level of 95 % as reported by the laboratories. The uncertainties also include the 1 % contribution resulting from the variability of the diameters of the syringes used. Figure 14 shows that the results of all laboratories are consistent when the stated uncertainties are taken into account. This is a confirmation that the different test procedures and uncertainty assessments used for the gravimetric measurements of the participating laboratories lead to consistent calibration results. To verify that the results are statistically consistent the normalised errors (En value) were calculated, showing that all values were below 1.2. (<1.2), thus confirming consistency.

From Figure 15 it can be seen, that error differences between the six liquids tested in the two laboratories do not exceed 1 % and are thus smaller than the stated uncertainties. To verify statistically that there is conformance between the results the normalised errors (E_n-value) were calculated, showing that all values were below one (<1.2), thus confirming consistency. The E_n-values were calculated according to the procedure described by Cox[23]. As a result, it can be concluded that there is no significant difference in the average flow rates generated by the syringe pump for the six liquids tested.

Insulin pumps

Insulin pumps can have different working principles and can operate at different flow rates. One working principle is an elastomer (like a balloon) that is filled with insulin and pumped through a capillary, providing a stable but fixed flowrate. Another principle is a linear actuator that drives a plunger in a cylinder, similar to a syringe pump. The latter type was used for the tests in this project[24].

[22] IEC 60601-2-24, Medical Electrical Equipment - Part 2-24: Particular requirements for the basic safety and essential performance of infusion pumps and controllers

[23] Cox M.G., Evaluation of key comparison data, Metrologia, 2002, 39, 589-595

[24] H. Bissig et al. Calibration of insulin pumps based on discrete doses at given cycle times. Biomed. Eng.-Biomed. Tech. 2022. https://doi.org/10.1515/bmt-2022-0040

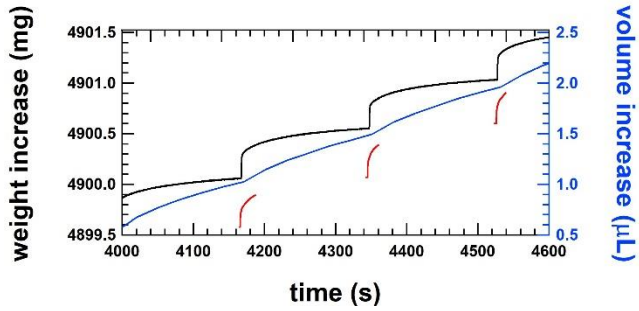


Figure 16: Smooth step increase of the weight of single shots of the order of 500 nL at a cycle time of 3 min for a flow rate of 10 µL/h or 1.0 U/h measured by the gravimetric setup at METAS (black line), by the front track setup at IPQ (blue line) and by the front track setup at THL (red line).

The delivery of discrete doses is visible in the raw data of the gravimetric method and the optical front track method, as shown in Figure 16. The weight increase of the gravimetric method shows a significant increase followed by a flattening of the curve before the delivery of the next dose (Figure 16, black line).

The same behaviour is observed for the front track methods, shown as blue and red lines. The red line is discontinuous because the optical front track method at THL is limited to a short measurement time and the gaps are the time needed for transferring the images to the PC. The blue line representing the position data of the optical front track method at IPQ shows step increases that are heavily smoothed out due to pressure relaxation in flexible tubing.

The method described in the standard IEC 60601-2-24:2012 – Clause 201.12.1.104[22] analyses the discrete volumes of the single doses at a constant cycle time. The method used in this work to analyse the discrete doses is very similar, except that the constant cycle time is replaced by the time stamps that identify the step increase in weight for the gravimetric method or the step increase in position for the front track method. The histogram of the weight increments at flow rate at 10 µL/h with the gravimetric method is shown in Figure 17, where the average of the discrete dose volume is 496.6 nL with a standard deviation of 21.2 nL, resulting in a deviation of +0.69 %. Furthermore, the corresponding cycle times of the discrete doses range between 179.80 s and 180.30 s with a mean value of 180.00 s.

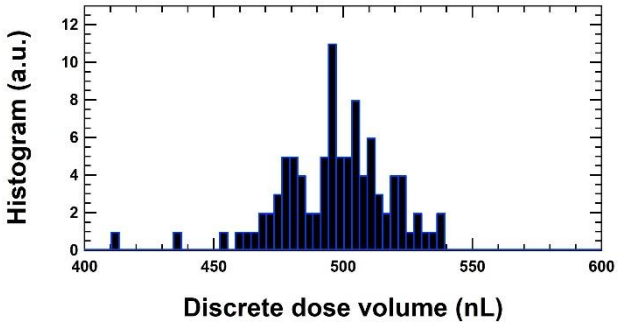


Figure 17: Histogram of dose volume measurements at METAS

The discrete dose analysis method is also suitable for determining bolus sizes or detecting irregularities from an insulin pump with its infusion set. However, the requirements of the measurement setup, such as the stabilisation time or the time frame for calculating an average value, must be respected in order not to misinterpret irregularities or malfunctions of the insulin pump.

Further analyses

Data from the measurement with the IDA and syringe pump were further analysed and presented in two open access papers[25] [26] published by the Journal of Biomedical Engineering.

The know-how and knowledge gained during the measuring campaign and analyses of the data were gathered in a guideline entitled ”Guidelines for the Calibration of Drug Delivery Devices and Infusion Device Analysers” by IPQ, CETIAT, HSG-MIT, DTI, CMI, STRATH, NEL, RISE and METAS. The guideline is intended as an official EURAMET guideline published on the EURAMET website, and therefore it was sent to the TC-FLOW group for publication approval. This approval is still pending.

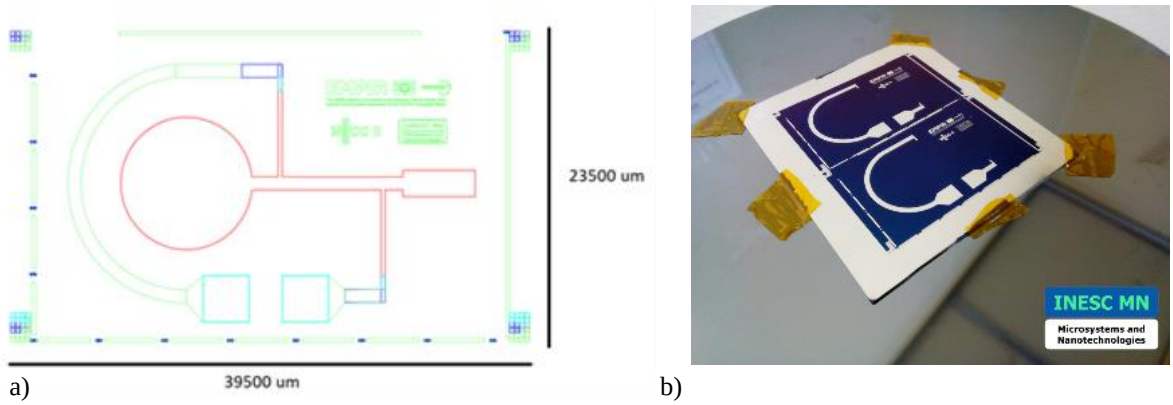
Microfluidic pump

A microfluidic pump was designed, and a numerical prototype of the pump was tested by INESC MN to prove the design of the pump. A physical prototype was developed and fabricated, see Figure 18. The design was documented in the report “*design document for a new mechanically active on-chip flow pump that will be*

[25] Assessment of drug delivery devices working at microflow rate, https://doi.org/10.1515/bmt-2022-0053

[26] Calibration of insulin pumps based on discrete doses at given cycle times, https://www.degruyter.com/document/doi/10.1515/bmt-2022-0040

integrated in a microfluidic device for use as a transfer standard in drug delivery and in organ on a chip application for flow rates lower than 100 nL/min" was finalised. This report can be found on the project webpage and in Zenodo. A paper on the development of this micropump [27] was also published by Journal of Biomedical Engineering.



a) b)

Figure 18: a) schematics of the chip with electrical contacts. green: electrical contacts $Al_{98.5}Si_{1.0}Cu_{0.5}$ (3000Å); red: cellulose membrane; light blue: passivation layer (Al_2O_3 3000Å); dark blue: TiW (300Å) + Cu (300Å) + graphene (monolayer) and b) chip with electrical contacts after microfabrication Step 5.

Summary

The metrology infrastructure for drug delivery devices that is already in place in hospitals, accredited laboratories and commercial companies/manufacturers has been identified. Thus, the gaps in metrological calibration procedures and traceability have been identified in order to develop relevant calibration procedures for drug delivery devices. An infusion device analyser, a clinically used syringe pump and an insulin pump have been extensively investigated at different flow rates with various liquids to improve the calibration procedures and to determine the uncertainty contributions of the calibration facility, procedure and the repeatability of the device itself. The knowledge gained about the improved calibration procedures was used to write a guideline entitled "Guidelines for the Calibration of Drug Delivery Devices and Infusion Device Analysers". This guideline was sent to the TC-FLOW group for publication approval (still pending) to become an official EURAMET guideline.

Moreover, a microfluidic electroosmosis pump was developed and produced as a prototype for steady and continuous fluid delivery for flow rates as low as 45 nL/min. These types of pumps can be used in microfluidic applications such as organ-on-a-chip or mobile healthcare systems. Overall, the objective was fully achieved.

[27] Development of a microfluidic electroosmosis pump on a chip for steady and continuous fluid delivery" Biomedical Engineering / Biomedizinische Technik, 2022. https://doi.org/10.1515/bmt-2022-0051

4.4 Objective 4: To design and develop a multi-infusion system containing check valves, with several options for testing how liquids, with different viscosities mix and flow and how this affects drug concentration. The flow rates and pressures will be traceably calibrated in all infusion lines, as well as at the outlet of the syringe pump, to be able to analyse the effects of pressure-equalising devices and to detect occlusion phenomena and bad mixing configurations.

The objective was to design and develop a multi-infusion system containing check valves, with several options for testing how liquids mix and flow and how this affects drug concentration in order to help end users build an optimal setup tailored to the needs of individual patients.

From the start it was known that the scientific state of the art and clinical practice have different starting points regarding flow rate accuracy. One of the challenges in the joint effort of metrologists and health professionals to improve dosing accuracy of individual medications in a multi-infusion setup, is the difference in the level of characterisation of these two parts of the setup. Whereas metrologists can specify and ensure stable lab conditions, the real-life setup under examination is not so well-characterised and at times also very dynamic. To ensure optimal cooperation using expertise from both worlds, a clear path was set from the start of the project integrating the knowledge generated from the other work packages in the development of the multi infusion system. In this approach, the tools from the well-defined metrological infrastructure, the tools created to develop a microchip pump and the new calibration tools of existing medical devices should be finally brought all together to design a metrologically sound characterised multi-infusion system for clinical practice. Therefore, a survey was conducted amongst clinical users of multi-infusion. It delivered responses from 15 participants, who were either doctors or nurses. It was confirmed that there are many different practices as it comes to building a multi-infusion setup. Therefore, five clinician face to face interviews have also been conducted to find the existing best practices. A summary report was made on the answers of the questionnaires and the interviews.

Based on the responses and UMCU's experience in multi-infusion practice, the development of the good practice guide was started. Note, the specific literature search on the best practice for infusion set-ups revealed that the descriptions were not as detailed as expected. Additionally, a literature review on viscosity effects and in-line air bubble effects was conducted. Using this work and the clinical physics experience from UMCU, THL, BHT, HSG-MIT, NEL, STRATH and METAS a list of the components required to prepare a clinically realistic setup for multi-infusion systems for drug delivery, as well as the test matrix to evaluate and characterise the typical multi-infusion system was decided on.

To characterise flow rates in a multi-infusion system, both a setup under investigation and a measurement system were defined (see Figure 19).

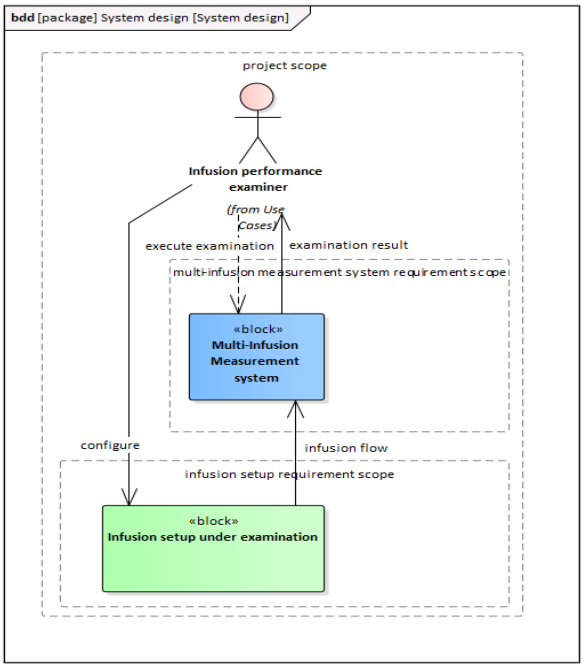


Figure 19: Definition of setup under investigation and a measurement system

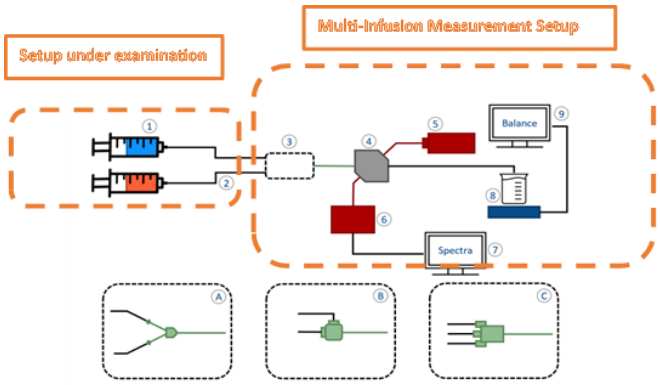


Figure 20: schematic of the measurement principle

Within the Metrology for Drug Delivery I[28] project an in-vitro setup was developed to illustrate the push-out effect and the effect of system mechanical compliance[29]. A schematic of the measurement principle can be found in Figure 20. The setup under examination can be changed according to the measurement needs. In Figure 20, three options for the set-up under examination are proposed according to its task to investigate mixing and drug concentration for various clinical applications: setup A contains a y connector catheter; set-up B uses a BD connector and set-up C a prototype component.

To characterise flow rates in a multi-infusion system, both a setup under investigation and a measurement system were defined. This test matrix was defined for three clinically realistic setups, based on a literature review and clinician interviews. Multi-infusion setups were built in Lübeck (THL) and in Utrecht (UMCU). The component list and setup were adapted for testing. At this point of the scientific research the COVID-19 pandemic started, creating a huge challenge to both the necessary lab access and getting the necessary clinical input.

In March 2020 all infusion pumps from the setups were claimed for COVID-19 care. Furthermore, experiments led by NEL and STRATH for investigating the impact of flow distortions caused by mechanical obstructions from components needed for the extension of the simulation model were delayed because of long-term laboratory access closure. The development of the prototypes was delayed as well. A mitigation plan was made, in which the researchers changed their focus to modelling using CFD, experiments without pumps or at alternative sites than at the UMCU hospital. The researchers available for the Metrology for Drug Delivery project who were not needed in the support of medical care utilised the available time for alternative work within the scope of the project, most importantly the MEDDII contributions to help fight COVID-19 by working out crisis & emergency practices for the medical community.

A fully integrated mass flow, pressure, density and viscosity sensor, capable of measuring concentrations of real drugs used in medical practice that was developed by Bronkhorst High Tech (BHT)[30], was integrated in one of the setups to add traceability of the flow rate of each component, and thus of the medication dose. The MEDD I in vitro setup used laser dyes mimicking the drugs and a spectrometer.

The predictive model of multi-infusion was extended to multiple flows and different viscosities. The basics of the model are described by Konings et al[31] and include the dead volume and push out effect, the effect of system mechanical compliance and resistance. Air bubbles and viscosity have been included in the model by UMC Utrecht.

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[28] Lucas, Peter and Klein, Stephan. "Metrology for drug delivery" Biomedical Engineering / Biomedizinische Technik, vol. 60, no. 4, 2015, pp. 271-275. https://doi.org/10.1515/bmt-2014-0155

[29] Timmerman, Annemoon M., Snijder, Roland A., Lucas, Peter, Lagerweij, Martine C., Radermacher, Joris H. and Konings, Maurits K.. "How physical infusion system parameters cause clinically relevant dose deviations after setpoint

[30] T. V. P. Schut, D. Alveringh, W. Sparreboom, J. Groenesteijn, R. J. Wiegerink and J. C. Lotters, "Fully integrated mass flow, pressure, density and viscosity sensor for both liquids and gases," 2018 IEEE Micro Electro Mechanical Systems (MEMS), 2018, pp. 218-221, https://doi.org/10.1109/MEMSYS.2018.8346523

[31] Konings MK, Snijder RA, Radermacher JH, Timmerman AM. Analytical method for calculation of deviations from intended dosages during multi-infusion. Biomed Eng Online. 2017 Jan 17;16(1):18. doi: 10.1186/s12938-016-0309-4. PMID: 2809585

A paper on the effects of air bubbles leading to unexpected dosing errors has been published in a special issue of Biomedical Engineering[32]. The predictive calculational model was extended further integrating a detailed analysis of the effect of check valves on drug delivery. To enable the validation of this model Computational Fluid Dynamics (CFD) simulations have been carried out by NEL. The CFD simulations led to the conclusion that the integration of a check valve into the infusion set-up causes a significant increase in the time needed for new medication to travel from syringe to patient. Konings et al. published a paper describing the effect[33].

In order to validate the model, replicas of the measurement system were sent to NEL and METAS. Using the model, it was found that parts of the measurement system can influence the setup under investigation in such a way that the measurement cannot give an adequate representation of it anymore. This was unfortunately true for the multiparameter sensor setup that was tested during this project. Though the setup had the capacity to measure viscosities and flow rates of different drugs inline in a mixture, because of the high resistance, it was not clinically representative. Measurement systems for use in clinical practice need to adapt their physical characteristics in such a way that they do not interfere with clinical requirements such as minimal start-up times. At the same time, it was established that for clinical practice, the accuracy needed from the sensors might be lower than can be achieved with these high-tech apparatuses as medical practice itself can be less accurate.

Therefore, the consortium chose to return to the measurement system using dyes and spectrophotometry that can deliver qualitative information on how infusion liquids mix and flow upon changes that are representative for clinical practice. Replicas of these setups, that were developed at THL and UMC Utrecht, were sent to NEL and METAS for metrological characterisation. Various experiments, where parts of the multi-infusion lines are investigated in isolated experiments or in a representative multi-infusion setup of clinical care, have been performed to validate the extended predictive model. In clinical application the pharmacokinetics play an important role and are therefore as important as the physical effects described in this validation report. Therefore, sometimes the phenomenological effects of the infusion setup are more important than the quantitative description and calculation of a realistic clinical multi-infusion setup. Nevertheless, it is important to point out that the quantitative effects of the extended predictive model are in clinically excellent agreement with the experiments preformed in the laboratory. Qualitatively, the various effects are perfectly described by the extended predictive model. Obviously, such detailed investigations are possible in preclinical work or R&D activities, but the reality of clinical practice is not reproducible in the laboratory.

In addition to the extension of the model and its validation, effort was made to provide physicians with a bed-side predictions tool (small computer attached to the multi-infusion set-up) that provides insight into the dosing errors that are to be expected after syringe exchange or changes in pump flow rate settings. A preliminary version of such a bed-side prediction tool was developed at UMC Utrecht.

A preferred way to share the outcome of metrological measurements is to use them in hands-on workshops where participants can try out the workings of the physical characteristics of the multi-infusion systems on real-life clinical setups using simple model fluids like water, milk, and coffee. Such a workshop was done at ESICM 35th LIVES conference at Paris for the Nurses and Allied Health Personnel community and it was well-liked by both nurses, pharmacists, doctors, and manufacturers.

A best practice guide on how to build an optimised multi-infusion set-up to ensure the most effective dosing of a combination of drugs was prepared from the starting point that such a guide has two typical recipients: clinical users and manufacturers. Guidelines on how to build a multi-infusion setup start from the patient needs. From there, choices must be made that balance clinical needs, pharmaceutical boundary conditions and the knowledge of metrological and physical principles found in this project. In the best practice guide on how to build an optimised multi-infusion set-up to ensure the most effective dosing of a combination of drugs and fluids with different viscosities, including guidance on check valves and other components that benchmark stability in flow rates"[34] guidelines are given that are applicable for general infusion therapy as well as guidelines that are connected to some specific patient applications. In this Best Practice Guide, the importance of cooperation of manufacturers, NMIs and end users was stressed to improve the dosing accuracy and to prevent morbidity due to the devices/delivery systems. Each actor has its place in the traceability chain, and this should be well established for the benefit of the patient. With this guide, the Metrology for Drug Delivery II

[32] Konings, Maurits K., Haaijer, Kelly, Gevers, Robin and Timmerman, Annemoon M.. "Unexpected dosing errors due to air bubbles in infusion lines with and without air filters" Biomedical Engineering / Biomedizinische Technik, 2022. https://doi.org/10.1515/bmt-2022-0056

[33] Konings, Maurits K., Gevers, Robin, Mejri, Sabrine and Timmerman, Annemoon M.. "Effect of non-return valves on the time-of-arrival of new medication in a patient after syringe exchange in an infusion set-up" Biomedical Engineering / Biomedizinische Technik, 2022. https://doi.org/10.1515/bmt-2022-0054

[34] https://zenodo.org/record/7417890#.Y8WIj9WZNaQ

Project has now provided the necessary tools to go forward in this cooperative direction to develop conditions for safe drug delivery.

Both guides are published on the project website and on Zenodo.

Summary

One of the challenges in the joint effort of metrologists and health professionals to improve dosing accuracy of individual medications in a multi-infusion setup is the difference in the level of characterisation. Metrologists can specify and ensure stable lab conditions for highly accurate measurements, but the real-life setup used by health professionals is not so well-characterised and at times also very dynamic. After a literature study, a questionnaire and face-to-face interviews with doctors and nurses investigating the best practice of building a clinically relevant multi-infusion setup, a list of components required for the build-up as well as the test matrix to evaluate and characterise these clinically realistic setups were compiled. Accordingly, the predictive model of multi-infusion was extended to multiple flows, different viscosities, effects of air bubbles and check valves. Various metrological experiments, where parts of the multi-infusion lines are investigated in isolated experiments or in a representative multi-infusion setup of clinical care, have been performed to validate the extended predictive model. It is worth to mention here that in-line sensors implemented in the multi-infusion setup for the characterisation of the setup might influence the physical behaviour of the setup if additional flow resistance or mechanical compliance are added. Therefore, only sensors with negligible flow resistance and mechanical compliance should be used for the experimental investigations. Moreover, in clinical applications the pharmacokinetics play an important role and are therefore as important as the physical effects described in the extended predictive model. Thus, the phenomenological effects of the infusion setup are more important than the quantitative description and calculation of a realistic clinical multi-infusion setup.
With this knowledge, the "best practice guide on how to build an optimised multi-infusion set-up to ensure the most effective dosing of a combination of drugs and fluids with different viscosities, including guidance on check valves and other components that benchmark stability in flow rates" has been written and includes guidelines applicable for general infusion therapy with multi-infusion set-ups as well as guidelines that are connected to some specific patient applications.
Overall, the objective was fully achieved.

5 Impact

The webpage developed during the EMRP JRP HLT07 MeDD (www.drugmetrology.com) was regularly updated with news and information such as project reports, articles/papers published by the partners and details of project meetings. The website had a large global reach with views from 91 countries. It had an average of 200 visits per month. A stakeholder committee (advisory board) was formed consisting of five members representing medical personnel and manufacturers of drug delivery devices. In terms of publications, 29 papers have been published in open access peer-review journals. The partners have made 39 oral and poster presentations to the scientific community or mixed audiences at international conferences. An article was published, and an interview was conducted for the public in the national press in North Korea by KRISS. A press release was prepared for the Journal of Anaesthesia Practice. Two articles were published in the Portuguese Magazine Tecno-Hospital magazine, and two articles were published by CETIAT one in DeviceMed magazine and the other in controles-essais-mesures magazine. Regarding standardisation, the consortium participated in several TC activities, namely: TC84/SC6 - ISO 7886-2, IEC/TC 62 D - IEC60601-2-24, ISO TC 48/WG3 - New ISO 22916 and ISO/AWI TS 6417, TC 48/WG4 – New ISO 8655-9, ISO 8655-1 and TR 20461, TC48/WG5 - ISO 23783-1,2 and 3, and ISO/AWI TR 6037, ISO/TC 150/SC 6 - ISO14708-4, AAMI TIR101 and TIR111, ISO TC 210 - ISO TR 24971 and ISO TC 212 – ISO 15189. Seven newsletters were published on the project's webpage. Two case studies were published on the webpage, namely: "A case study on COVID-19 crisis & Emergency Practices with Infusion Pumps in ICU, the role of Metrology" where our project and this document were recognised as relevant by the European Commission (EC) and is now also available on the EC website and in a report on "Measurement error: two opposite definitions". Two online workshops were conducted, one on the 18th of November 2020: "Microflow calibration methods" with 5 oral presentations and another on 15th of September 2021 organised in cooperation with Lübeck University: 14th Lübeck Workshop "Low Liquid Flows in Medical Technology" with 6 oral presentations from the project participants. Two webinars were developed by NEL and CETIAT during 2021 for a predominantly industrial audience with more than 50 participants in each webinar. Several activities were developed under the 2021 Metrology Day, that was dedicated to measurements in health, namely a flyer and a good practice guide for the Calibration of Medical Infusion Pumps along with a video on Traceability of infusion pumps. In September

2021 a video on the Calibration of drug delivery devices was also developed. A final workshop of the project was given in November 2022. The first day was dedicated to Traceability, application and use of drug delivery devices and had 6 invited presentations from the medical community (the presentations are available on https://drugmetrology.com/workshop-on-the-importance-of-metrology-and-traceability-in-drug-delivery-devices-online-event-day-2-material/) and the second day was dedicated to the presentation of the project results and the presentations are available here https://drugmetrology.com/workshop-on-the-importance-of-metrology-and-traceability-in-drug-delivery-devices-online-event-day-2-material/.

A PhD by Elsa Batista was performed and concluded during this project namely "Innovative contributions on calibration methodologies towards reliable microflow measurements" by the University FCT /UNL in Lisbon. http://hdl.handle.net/10362/134197

A Special issue of the Journal Biomedical Engineering - Title "Medical flow and dosing measurement metrology in drug delivery" was prepared with 10 papers (February 2023, Issue 1/2023).

All data and relevant publications are available on the Zenodo repository under the Metrology for Drug delivery community (MeDD2).

Impact on industrial and other user communities

This project created impact as new calibration services were developed that are of direct relevance to the project's industrial and other user communities. These new calibration services include steady flow rates and fast changing flow rates, which are of benefit for the characterisation of drug delivery devices, for the accuracy of the flow rates delivered, for the effective delivered volumes and for the response times to flow rate changes. These characteristics are traceable, and it is possible to compare them directly with the characteristics of other products (using datasheets). The project's industrial and other user communities can test and improve their drug delivery devices or develop new devices with increased accuracy.

An online workshop was delivered on the 18th of November 2020: Microflow Calibration Methods, five presentations on the different calibration methods were performed by the consortium. This workshop had more than 70 participants (Partners, Industry, Academia) and they gave very positive feedback on the event.

Another online workshop was delivered on the15th of September 2021 organised in cooperation with Lübeck University: 14th Lübeck Workshop "Low Liquid Flows in Medical Technology" with 6 oral presentations from the consortium. This workshop had also more than 70 participants (Partners, Industry, Academia).

Two webinars were developed by NEL and CETIAT during 2021 for a predominantly industrial audience with more than 50 participants in each webinar.

A training course on metrology for drug delivery, was held online on the 21st of June 2022 by IPQ in Portuguese. More than 50 participants from the medical field attended the training course. This event addressed among other issues the best practices for the use of medical devices, the legal and normative documents and the calibration procedures for drug delivery devices. Presentations were given by Elsa Batista and Maria do Céu Ferreira. A discussion forum was held at the end of the presentations.

A training course on Metrology for drug delivery was held online on the 8th of September 2022 by NEL and CETIAT. In total more than 50 participants from the medical field attended. The presentations are available on the project webpage.

UMC Utrecht provided an onsite workshop on drug delivery for medical personnel at ESICM Lives on October 22-26, 2022, Paris with 25 participants. UMCU also gave several workshops to the Wilhemina Children's staff Hospital, on site, with a total of 40 participants.

In total the training workshops for users done by this project had more than 200 participants, from nurses, doctors, maintenance officers of hospitals and regular hospital staff. The feedback from these workshops allowed us to conclude that the impact was very good.

The final project Workshop was held online on 23rd and 24th November 2022 with more than 50 participants and 12 speakers, organised by IPQ and CETIAT. The first day was dedicated to end users in the medical world and the second day was dedicated to the dissemination of the project's outcomes.

The new calibration service for in-line measurements of dynamic viscosity, pressure and flow rate is creating impact as these measurements allow the investigation of the effects of viscosity, pressure and flow rate on the performance of the drug delivery devices, flow generators or flow meters. These characteristics are traceable, and it is possible to directly compare them to the characteristics of other products. This enables clinicians to better select appropriate products for the intended applications. R&D laboratories are also benefitting as they are able to improve their products or testing facilities.

Improved calibration procedures for drug delivery devices are creating impact as the increased calibration accuracy allows the systematic uncertainty contributions to be decreased.

The systematic testing, of a clinically representative in-vitro multi-infusion intravenous system, for potentially fatal dosing errors, led to deeper knowledge of the influence of each of the system's components and their combinations. This project created impact by transferring this knowledge to users of infusion technology so that they can reduce the number of fatal dosing errors. By improving flow measurements, and reducing dosing errors, lives can be saved, and this is the ultimate impact of this project.

Impact on the metrology and scientific communities

This project created an early impact as it allows NMIs to upgrade their existing facilities for flow measurements from 5 nL/min up to 100 nL/min using different fluids with differing properties and this resulted in new calibration services for customers. The new traceability chain and primary standards were validated through an inter-comparison with stable transfer standards in order to provide new measurement capabilities.

Several end users/manufactures have asked several partners (like IPQ, METAS, CETIAT and RISE), which have updated and published their new CMCs in the KCDB during 2022, to calibrate their drug delivery devices. For example: Metas had more than 20 requests for the calibration of instrument devices analysers (IDA), IPQ had more than 6 calibration requests for these IDA and two for syringe pumps, CETIAT had more than 20 syringe pumps calibration requests and an insulin pump calibration was also performed.

New optical-based calibration methods were developed, and impact was created as these methods were disseminated to the scientific community in relevant publications and events. These new calibration methods will be beneficial for both accredited laboratories and manufacturers of drug delivery devices. These new procedures can be updated later for the microfluidic devices used in healthcare, i.e. mainly in the organ-on-a-chip technology. A calibration guide for the different types of drug delivery devices was developed and it describes the different calibration methods, the conditions under which they must be operated, the target uncertainty and the best working practices. This document was submitted to EURAMET TC F and it will be made available to end users.

Seven newsletters were developed and are now available on the project webpage.

The generated data is now available on the Zenodo repository under Metrology for Drug delivery community (MeDD2) and it is open to the whole community.

Impact on relevant standards

In this project, procedures and methods for the calibration of drug delivery devices that are already on the market were developed. The consortium created impact by supplying this information to the relevant ISO technical committees (TC) and endeavoured to ensure that these results are incorporated in any updates to standards (e.g. IEC 60601-2-24, ISO 7886-2 and ISO 8655-9) or guidelines. For example, the current version of IEC 60601-2-24, which is used by manufacturers to develop drug delivery devices and by laboratories and hospital maintenance departments to verify and calibrate drug delivery devices is outdated as the edition is from 2012. Moreover, the stated measurement methods are not suitable for the very low flow rates (< 100 nL/min) that are relevant to implantable infusion pumps. The urgent need to update the measurement procedures for different types of pumps and master calibrators is widely accepted. It is expected that this

project will impact Section Eight (Accuracy of operating data and protection against hazardous output) of IEC 60601-2-24. Contact has been established with TC62/SC62D/MT23. The comments on IEC60601-2-24, given by the consortium, were discussed and implemented. This standard entered the revision stage in 2020 and the partners followed its progress but the revision stopped due to the resignation of the chair. ,During this time, in November 2021 an AAMI TIR 101 - Fluid delivery performance testing for infusion pumps was developed and published with the cooperation of several MeDDII partners.

Input was provided for use in Regulation (EU) 2017/745 of the European Parliament and of the Council of 5 April 2017 on medical devices as it is currently lacking information regarding the maximum permissible errors and other relevant information, like safety aspects and risk evaluation. A report on Drug Delivery Devices safety and use – the role of the medical devices regulation was developed by the consortium, it was sent to the regulators of each country partner and to the EU and its available on Zenodo.

Regarding standardisation, several other activities were engaged, namely in TC84/SC6, where a contribution was given to ISO 7886-2 and this standard was published in 2020.

A new ISO 8655-9 for syringe calibration and ISO 8655-1 Vocabulary, under ISO TC 48/WG4 are now published. IPQ followed this work and was the project leader. NQIS also participated as a representative of EURAMET. The ISO TR 20461 for uncertainty calculation of volume gravimetric method is also under revision under this TC and IPQ is the project leader. The new ISO 22916 is now published, and ISO/ TS 6417 has been developed with the cooperation of several partners from the project under TC48/WG3. Also, under TC 48/WG5 the new ISO 23783-1, 2 and 3 were developed with the contributions from this consortium and are now published. The partners also provided contributions to ISO/AWI TR 6037 – Automated liquid handling systems – Uncertainty of the measurement procedures.

ISO/TC 150/SC 6 has started the revision of ISO 14708-4 and the consortium has sent comments to the document. The document was published in 2022.

ISO TC 210 has finalised the work on ISO TR 24971:2019 and the standard in now published.

ISO/TC 212 has started the revision of ISO 15189 and the consortium has sent comments on the document.

A new AAMI TIR 111 is now under development with the cooperation of the MeDDII consortium.
EURAMET has published a case study on the project MeDDII concerning our collaboration with standardisation in the revision of the relevant standards for syringe pump testing.

Longer-term economic, social and environmental impacts

This project directly benefitted society by enabling the identification and reduction of dosing errors in drug delivery devices that are used for patient treatment and diagnostics.

By improving the accuracy of instruments, dosing errors were reduced, and lives will be saved. This was achieved through wider uptake of traceable calibrations of low and ultra-low flow infusion (master) devices and improved knowledge of drug delivery device calibration in the clinical environment, particularly for multiple infusion systems.

6 List of publications

1) "Method selection to evaluate measurement uncertainty in microflow applications" published in Journal of Physics https://doi.org/10.1088/1742-6596/1379/1/012033

2) "Calibration of Insulin Pumps" published in Journal of Diabetes and Treatment https://www.gavinpublishers.com/assets/articles_pdf/1575449809article_pdf938882132.pdf

3) "New EMPIR project – Metrology for Drug Delivery" published in Flow measurement instrumentation https://doi.org/10.1016/j.flowmeasinst.2020.101716

4) Traceability of pulsed flow rates consisting of constant delivered volumes at given time interval published in Flow measurement instrumentation https://doi.org/10.1016/j.flowmeasinst.2020.101729

5) Development of an optical measurement method for "sampled" micro-volumes and nano-flow rates. Measurement and Instrumentation, https://doi.org/10.1016/j.flowmeasinst.2020.101746

6) Development of an experimental setup for microflow measurement using interferometry published in Flow Measurement and Instrumentation https://doi.org/10.1016/j.flowmeasinst.2020.101789

7) Calibration of Syringe Pumps Using Interferometry and Optical Methods published in the International Journal of Biomedical and Biological Engineering https://publications.waset.org/10011517/pdf

8) Improving infusion dosing accuracy for patient safety, European Pharmaceutical Review, Volume 26, Issue 04, ISSN 1360-08606 https://www.europeanpharmaceuticalreview.com/article/160985/european-pharmaceutical-review-issue-4-2021/

9) Ultra-low flow rate measurement techniques, Measurement: Sensors, 18, 100279, https://doi.org/10.1016/j.measen.2021.100279

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11) Uncertainty calculations in optical methods used for micro flow measurement, Measurement: Sensors, 18, 100155 https://doi.org/10.1016/j.measen.2021.100155

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