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Metrology for Drug Delivery project – results and impact

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Abstract

This paper presents the major impacts of the work developed in EMPIR Project - MeDD II, Metrology for Drug Delivery in the reference standards used for flow rate determination of drug delivery devices and the results obtained in each work package, with a special focus on the primary standards developed by the partners using different technologies. These new primary standards were validated via an inter-laboratory comparison using two different type of flow meters and a precision syringe pump, in a range from 1500 nL/min down to 5 nL/min. This inter-comparison was performed between nine participating laboratories, each with different methodologies, measurement principles, flow ranges, operating conditions, and measurement uncertainty values.

1. Introduction

Flow measurement is critical in healthcare, chemistry and pharmaceutics, to mention a few applications. In fact, there are several applications in the microflow and nanoflow range, such as scaled-down process technology, drug development, and special health-care applications, such as organ-on-a-chip technology. Nevertheless, the majority of the instruments used for the specified applications are not sufficiently studied regarding their flow accuracy and traceability. Hence these fluid applications at the micro and nanoscale still lack well defined calibration methodologies for the devices working at the mentioned flow range with adequate uncertainty values.

The EMPIR Project - MeDD II, Metrology for Drug Delivery [1], funded under the EMPIR program of the European Commission, started in June 2018, with the evolvement of 16 partners including: nine National and Designated Metrology Institutes (IPQ – Portugal, CETIAT – France, CMI – Czech Republic, DTI - Denmark, METAS – Switzerland, NEL – United Kingdom, NQIS – Greece, RISE – Sweden and KRISS - Korea), four companies (DNV GL – The Netherlands, HSG-IMIT – Germany, INESC MN – Portugal, BHT – The Netherlands, and 3 universities, THL – Germany, UMC Utrecht- The Netherlands and the University of Strathclyde from Scotland and has the overall aim to improve dosing accuracy and enable traceable measurements of volume, flow and pressure of existing drug delivery devices and inline sensors operating at very low flow rates (lower than 100 nL/min). This can be achieved through the development of new calibration methods and improved metrological infrastructures. Another goal of this project is to investigate the influence of different flow rate regimes, physical properties of the infused fluids (e.g. viscoelasticity), and occlusion phenomena in multi-infusion systems. This knowledge will help preventing inaccurate measurement results and thus improve patient safety. The project was divided into 4 technical work packages, an impact work package and a coordination work package.

2. Developments done in WP1

The aim of this work package 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 developed techniques have been used to characterise and validate the response times of the different types of drug delivery devices used in WP3 and WP4. The uncertainty targets depend on whether the measurement mode is for a steady flow rate or for a fast changing flow rate. For a steady flow rate an uncertainty of 1 % (k=2) or better is

targeted, whereas for a fast changing flow rate an uncertainty of 2 % (*k*=2) or better is targeted. This was achieved by building on the knowledge gained in EMRP JRP HLT07 MeDD, either by developing new techniques or by adapting existing primary standards to meet these goals. The new traceability chain and primary standards have been validated with an inter-comparison, followed by the new Calibration and Measurement Capabilities (CMCs) being published in the BIPM database.

Concerning this WP outputs, the development of metrology infrastructure for ultra-low flow rates was concluded. A comprehensive report produced on the new calibration methods for steady and dynamic flow rates was developed and is available on the project webpage as deliverable 1 [2].

Several new techniques were developed, mainly front track, interferometry and micro PIV. Also, already implemented techniques like the gravimetric method were improved [3] (Figure 1).

Figure 1. Micro flow calibration techniques. Left: interferometric method. Middle: volumetric method. Right: pendant drop and front track method.

A comparison with the aim of validating the measurement methods for static and dynamic tests defined above, with 9 partners participating, has been concluded and the final report published under EURAMET project 1508 [4]. A Sensirion meter, a Bronkhorst meter and a Cetoni precision syringe pump were tested at different flow rates. 90% of the results were satisfactory with a degree of equivalence (En) below 1. The results are presented in the following figures.

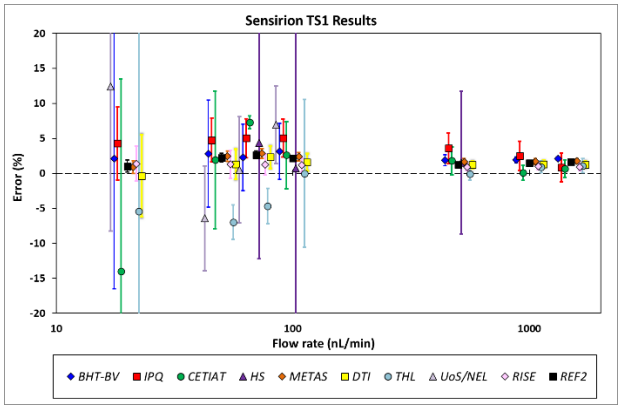

Figure 2. Inter-laboratory comparison results for Sensirion meter

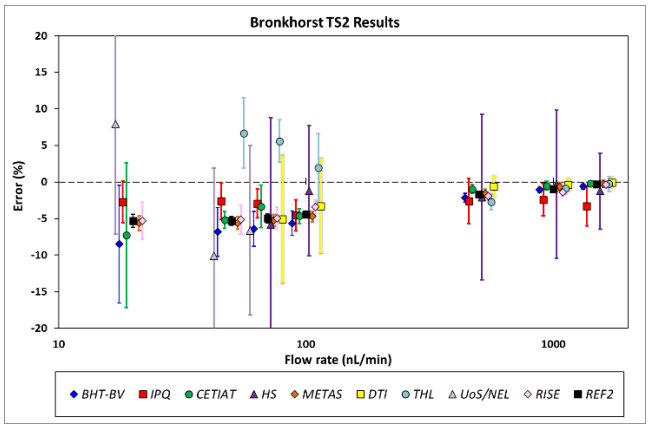

Figure 3. Inter-laboratory comparison results for Bronkhorst meter

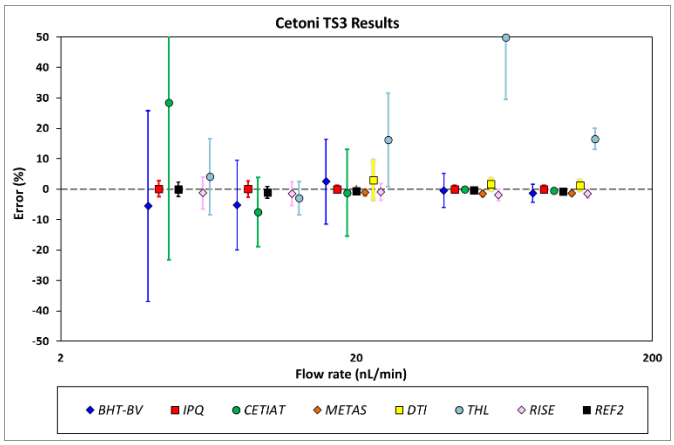

Figure 4. Inter-laboratory comparison results for Cetoni pump

CMCs for microflow measurements were submitted by IPQ, METAS, RISE and CETIAT to the KCDB in 2022.

3. Developments done in WP2

The aim of this work package was to provide traceable in-line measurement of the physical and thermodynamic properties of single and multi-component liquids at steady flow rates. three primary standards for the in-line measurement of dynamic viscosity have been developed by applying the principle of a pipe viscometer with a target uncertainty (*k*=2) less than 2 %. The pipe viscometer is based on the measurement of the pressure drop over a defined length in a straight pipe, the flow rate and the liquid temperature. The pressure, flow rate and temperature have been selected to meet clinical requirements. The viscosity has then been determined from a physical model including several empirical corrections.

Regarding the achievements of this WP, the primary standards for in-line measurements of dynamic viscosities have been developed at RISE, NEL and METAS (figure 5).

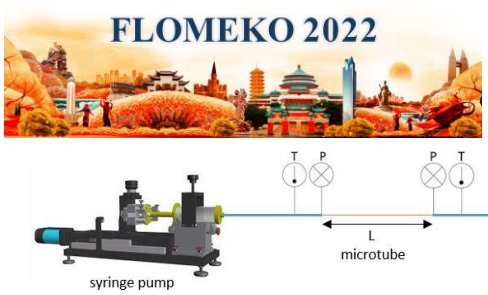

Figure 5. Pipe Viscometer consisting of a piston prover and a micro tube with pressure and temperature sensors upstream and downstream of the micro tube.

Calibrations of the dynamic viscosity of reference oils with traceable densities and viscosities measurements were used for the validation of the stated uncertainties of the pipe viscometers.
Additionally, eight different liquids used in medical applications have been measured by pipe viscometers, glass capillary viscometers (commercially available instruments) or rotational viscometers. These measurements underline the validity of the stated uncertainties and the measurement procedure of the newly developed pipe viscometers (figure 6).

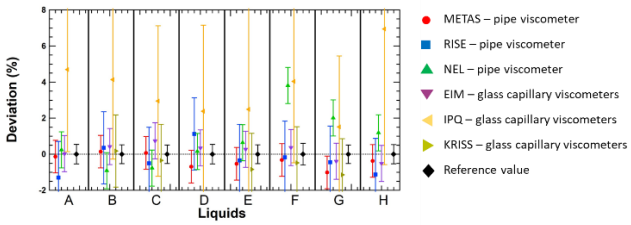

Figure 6. Comparison results of viscosity of different liquids measured by several partners using different methods.

4. Developments done in WP3

The aim of this work package was to develop calibration methods and procedures for existing drug delivery devices e.g. insulin pumps, pain pumps and a new prototype on-chip pump. Traceable primary standards, based on gravimetric techniques, PIV and optical methods, have been established with uncertainties less than 2 % for a flow rate range of 5 nL/min up to 600 mL/min. The procedures are used to develop a new EURAMET guideline and as input to ISO standards.
Once the prototype on-chip pump has been developed, corresponding calibration procedures will be developed. This pump will be used as a traceable primary standard for the calibration of the drug delivery devices that are used for flow rate ranges from 5 nL/min to 100 nL/min, with a target uncertainty of 2 %.
Regarding the outcome of this work package a design for a microfluidic pump has been developed and a numerical prototype of the pump has been tested to prove the design. A physical prototype has been produced (Figure 7) and design document (deliverable 5) is available on the project website [2].

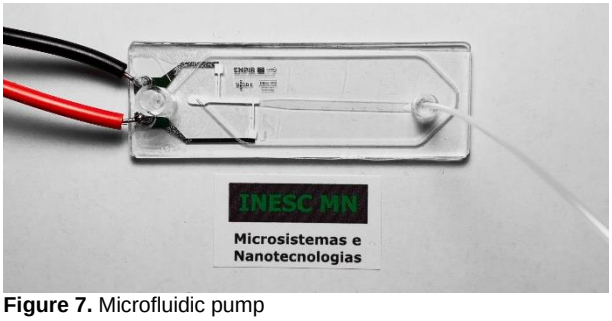

Figure 7. Microfluidic pump

Regarding the development of calibration procedures for drug delivery all the tests were performed and a EURAMET guide is under preparation. The instruments tested were an insulin pump, an infusion device analyser (IDA) and a syringe pump (figure 8).

Figure 8. Medical devices characterized during WP3. Left: insulin pump. Middle: Infusion Device Analyzer. Right: syringe pump.

5. Developments done in WP4

The aim of this work package was to design a clinically representative in-vitro multi-infusion intravenous (IV) system that are used to investigate how liquids with different viscosities mix and flow, and how this affects the effective drug concentration over the time of delivery. The flow rates and pressures are traceably measured in all infusion lines, as well as at the outlet of the syringe pump. With this new in-vitro multi infusion system, the effects of prototype pressure-equalising devices and check valves (that prevent the backflow of fluids), can be assessed, as well as the effects of mixing configurations. Furthermore, the pressure effects of clinically relevant occlusion phenomena is characterised to enable reliable, pressure based, occlusion alarm systems to be developed/used.
In this WP multi-infusion setups were built in Lübeck (Germany) and in Utrecht (Netherlands). Figure 9 shows a multi-infusion setup with a flow cell to measure the ratios of the different coloured (dye) liquids by means of a spectrometer and the absolute flow rate by either a mass flow meter or the gravimetric method.

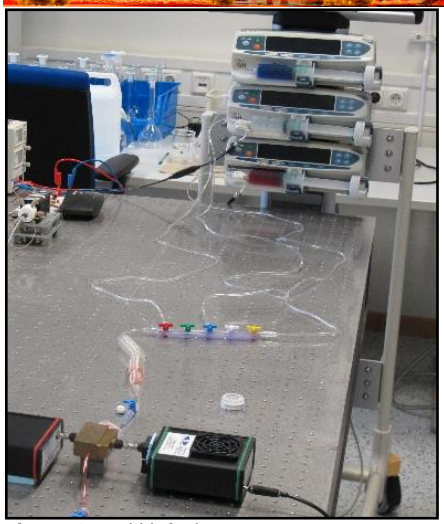

Figure 9. Multi infusion setup at THL.

The predictive model of multi-infusion was extended to multiple flows and different viscosities, where the influence of compliance, dead volume, Poiseuille flow effects, push out effects, RC response times of the setup are taken into account. All separate effects are joined together into one comprehensive model. Additionally, consequences of air bubbles in a line with an air filter are also investigated as well as flow distortion due to check valves in the lines. Replicas of different multi-infusion setups have been sent to NEL and METAS for model validation measurements.

6. WP 5 - Impact

The aim of this work package was to facilitate the uptake of the technology and measurement infrastructure developed in the project by the measurement supply chain (accreditation laboratories, instrument manufacturers) and end users (hospitals). It will also support the development and revision of standards (e.g. ISO standards), guidelines for harmonised drug delivery device testing and uncertainty estimation and it will provide input to improve regulations.
MeDD II participants are actively engaged with the impact on standardization namely ISO 8655-9 that was published in April 2022, ISO/DIS 23783-1,2 and 3, ISO/DIS 22916 and ISO/AWI TS 6417 from ISO/TC 48, ISO 15189 from ISO/TC 212. The TIR 111 - Fluid delivery performance testing for infusion pumps from AAMI was published in November 2021, including valid definitions of fluid delivery performance test methods for all infusion pump use conditions. This standard provides clinically relevant performance data, including reference to EURAMET's Calibration Guide No. 19 [5]. The 'MeDDII project contributed significantly to the metrological information and technical requirements added to the document.
29 presentations were done in conferences and 12 papers published in peer review magazines. Several good practice guides, videos and case studies were produced and are available on the project webpage.
Highlighting the role of the regulation 2017/745 on medical devices that entered into force on 26th May 2021, the MEDD II consortium gave an outlook and a quick landscape review within the relevance of metrological requirements of infusion devices to provide a better shared understanding of this issue. To this end, a report on Drug Delivery Devices safety and use – the role of the medical devices regulation was developed and published on the project webpage.

7. Conclusions

The main objectives of the project MeDDII were accomplished, and it was possible to develop and validate microflow primary standards down to 5 nL/min with 2 % uncertainty (k=2), and CMC were submitted to the KCDB - Key Comparison Database of BIPM. Measurements of inline liquid proprieties were performed, and a new microfluidic pump fabricated. Characterization tests were performed in several drug delivery devices and a EURAMET guide is under development. Multi-infusion setups were developed and validated and finally the outputs of the project were disseminated to 9 ISO technical committees and at the AAMI group. All the work done in the project can be obtained on www.drugmetrology.com

Acknowledgements

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References

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