
Publishable Summary for 18HLT08 MeDDII Metrology for Drug Delivery

Overview

The overall aim of this project is 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 will be achieved through the development of new calibration methods and by expanding the existing metrological infrastructure. This project will also investigate 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 will improve patient safety.

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 is therefore an urging need to prevent these adverse incidents, morbidity and mortality, which are 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 are 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 is 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 will enable users to have better metrological knowledge of the devices, preventing incorrect measurement results. Ultimately this will result 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, is based on the design of a representative multi-infusion system to test how different liquids mix and how this affects the drug concentration. The goals of this project already foresee the increasing implementations of novel microfluidic solutions in healthcare, which will require the development of a metrological infrastructure for validating quality and reproducibility.

Objectives

The overall objective of this project is 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 will also investigate 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 are:

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).

Progress beyond the state of the art

In 2004, a metrological effort to understand and improve multi-infusion, defined the crucial performance aspect of an infusion system and established the importance of a patient receiving the right dose of the required substances in a given time. However, in multi-infusion, this is not an easy task. The first steps towards better knowledge of the real flow rates and concentrations of drugs delivered to the patients' blood stream were made in previous projects. In EMRP JRP HLT07 MeDD the aim was to prevent errors by upgrading calibration services and improving knowledge transfer to the end-user. The infrastructure, consisting of traceable calibration services for drug delivery systems for flow rates down to 100 nL/min was developed in five European National Metrology Institutes (NMIs). Syringe pumps and peristaltic pumps with accessories were tested. The effects of variations in several physical parameters in infusion systems were incorporated in a predictive model.

This new project will go beyond the research conducted in EMRP JRP HLT07 MeDD by investigating the influence of the fast changing flow rates that result from a change in the pre-set flow rate. It will develop new traceable techniques for generating and measuring the response or delay time of drug delivery devices in relation to changes in flow rate, from 5 nL/min to 100 nL/min.

Concurrently, the existing flow facilities at the participating NMIs will be upgraded to enable the traceable in-line measurement of the dynamic viscosity of Newtonian liquids (Dopamine, dobutamine and saline solution), based on flow rate and pressure drop. These investigations will help to prevent dose fluctuations and they will improve occlusion alarm reliability.

Furthermore, novel flow and volume measurement methods and calibration procedures for existing drug delivery devices (e.g. insulin pumps, syringe pumps, infusion device analysers and pain pumps), micro-chip pump devices and in-line sensors operating at very low flow rates, i.e. < 100 nL/min, will be developed. The new measurement methods are based on optical, interferometry and microPIV (Particle Image Velocimetry) technology.

Also, a multi-infusion setup will be developed to investigate fluid flow rates and fluid compositions in the outlet of the infusion line. This setup will allow the assessment of the performance of drug delivery devices in multi-infusion systems and the determination of the concentration of each drug being administered.

The knowledge gained in this project will enable the prediction models developed in EMRP JRP HLT07 MeDD to be upgraded by adding the effects of check valves and some of the physical properties of the flowing fluids (e.g. viscosity). This new model will reflect a more realistic mixing behaviour in the infusion lines and it will be validated by experimental results.

Various studies of the different methods that are used to measure volumes at the nanolitre scale have recently been published. These methods use quartz crystal microbalances, capacitive droplet sensors, and air flow sensors that hold the promise of providing an accurate and cost-efficient measurement method to be integrated into liquid handling instruments for on-site calibration and verification. Although various promising measurement methodologies have been demonstrated experimentally, metrological validation (including traceability to primary standards) of these methods still needs to be achieved, and that is one of the main goals of this project.

Results

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.

The majority of the partners have concluded their development of new methods for the measurement of microflow down to 5 nL/min. Different techniques have now been implemented by the partners. By using different flow generators they were able to achieve different flow intervals with different uncertainty levels:

- METAS is now using a piston prover generating flow down to 20 nL/min with a relative uncertainty of 0.65 %;
- DTI is using a gravimetric method down to 16 nL/min with a 4 % relative uncertainty;
- IPQ developed an interferometric-based method that is able to measure flow down to 5 nL/min with a 3 % relative uncertainty;
- NEL and HSG-MIT are using an optical nanoflow measurement technique based on microPIV, which is expected to go down to 1 nL/min;
- CETIAT has extended the front track principle down to 5 nL/min with a 0.5 % uncertainty;
- THL has rebuilt its front tracking principle to a more mechanically robust design and extended down to 5 nL/min;
- CMI has developed an improved beaker for the gravimetric method with conclusive testing in progress to finalise the design.

The uncertainty budgets are now completed for each method and this information was included in the first deliverable of the project - 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, which is available on the project webpage (www.drugmetrology.com).

An interlaboratory comparison protocol has been developed and the measurements will start in January 2021. This comparison has the purpose of validating the developed measurement methods for static and dynamic tests. 10 partners will participate in this comparison. The transfer standards chosen are the thermal flow meter L01 from BHT (1500 nL/min to 20 nL/min) the SLG-0075 (1500 nL/min to 20 nL/min) from Sensirion AG and a Cetoni syringe pump (100 nL/min to 5 nL/min).

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.

Two questionnaires for clinical users of multi-infusion setups, for technicians using multi-infusion setups and for manufacturers of drug delivery devices were developed and circulated. 15 answers were obtained from clinicians and 18 answers were obtained from manufacturers; this enabled the identification of the clinically relevant interval for the dynamic viscosities (< 2 mPa s), the pressure range (0.1 bar – 0.5 bar) and for the flow rates (from 1 μ L/min to 10 mL/min). Based on the questionnaires, and discussions at the M9 meeting in February 2020, the liquids to be tested in the next task have been chosen, namely saline solution, dopamine and dobutamine. However, these drugs are not easy for some of the laboratories to obtain. Therefore, validation measurements with saline solutions and glucose solutions (various concentrations) and mixtures are planned to compare the performance of the different pipe viscometers. Measurements with reference oils of calibrated densities and viscosities underline the feasibility of the pipe viscometers with the target uncertainty of 1 % ($k=2$). Several in-line devices have been identified and will be used in the subsequent tasks.

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.

From the questionnaire and with inputs from collaborators and stakeholders, the relevant types of drug delivery device and flowrate intervals have been identified. A protocol for testing and to define calibration procedures for the drug delivery devices has been developed. The measurements started in October 2020 and are expected to end in June 2021. The chosen instruments to be tested were an insulin pump, an implantable pain pump, a syringe pump and an Infusion pump analyser.

The microfluidic pump has been designed and a numerical prototype of the pump has been tested to prove the design by INESC MN. A physical prototype is under development and fabrication.

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.

So far 15 responses from the questionnaire and five clinician face to face interviews have been conducted. A summary report on the answers of the questionnaires and the interviews has been completed and the consortium has agreed on a list of components and a test matrix.

The best practice guide, based on the answers from the questionnaires returned so far and UMCU's multi infusion practice experience, is under development. 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.

The list of components required to prepare a clinically realistic setup for multi-infusion drug delivery systems and of the test matrix to assess and characterise the typical multi-infusion system are now available.

Multi-infusion setups were built in Lübeck and in Utrecht. The component list and setup were adapted for testing and the sensor integration is currently on schedule. The development of the prototypes has been initiated, as well as the flow cell development.

The predictive model of multi-infusion was extended to multiple flows and different viscosities. Air bubbles and viscosity have been included in the model by UMC Utrecht. To enable the validation of this model Computational Fluid Dynamics (CFD) simulations are under development by NEL. The incorporation of check valves in the model has also started.

Impact

The webpage developed during the EMRP JRP HLT07 MeDD (www.drugmetrology.com) is regularly updated with news and information such as project reports, articles/papers published by the partners and details of project meetings. Since the project start date (1st June 2019) the website has been viewed 1847 times. The website has a large global reach with views from 91 countries. A stakeholder committee (advisory

board) has been formed consisting of five members representing medical personnel and manufacturers of drug delivery devices. In terms of publications, 7 papers have been published in open access peer-review magazines. The partners have made 15 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. 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/WG4 – New ISO 8655-9, TC48/WG5 - ISO 23783-1,2 and 3, ISO/TC 150/SC 6 - ISO14708-4, AAMI TIR101 and ISO TC 210 - ISO TR 24971:2019. Two 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", Our project and this document was recognised as relevant by the European Commission (EC) and is now also available in the EC website. "The role of Metrology and a report on Measurement error: two opposite definitions". An online workshop was conducted on the 18 of November 2020: Microflow calibration methods with 5 oral presentations. All data and publications are also available on the Zenodo repository under the Metrology for Drug delivery community (MeDDII).

Impact on industrial and other user communities

This project will create impact as new calibration services will be developed that are of direct relevance to the project's industrial and other user communities. These new calibration services will include steady flow rates and fast changing flow rates, which will be 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 will be traceable, and it will become possible to compare them directly with the characteristics of other products (using datasheets). The project's industrial and other user communities will also be able to test and improve their drug delivery devices or develop new devices with increased accuracy.

An online workshop was delivered on 18th 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 a very positive feedback on the event.

Another new calibration service will create impact as it will allow the effects of viscosity, pressure and flow rate on the performance of the drug delivery devices, flow generators or flow meters to be tested. These characteristics will be traceable, and it will be possible to directly compare them to the characteristics of other products. This will enable clinicians to better select appropriate products for the intended applications. R&D laboratories will also benefit as they will be able to improve their products or testing facilities.

Improved calibration procedures for drug delivery devices will create impact as the increased calibration accuracy will allow systematic uncertainty contributions to be decreased. These systematic contributions might be caused by a coincidence of the measurement principle of the device and the calibration method, which induces additional deviations. This might be because the calibration method is not appropriate or because it does not respect the specifications of the manufacturer's operation manual.

The systematic testing, of a clinically representative in-vitro multi-infusion intravenous system, for potentially fatal dosing errors, will lead to deeper knowledge of the influence of each of the system's components and their combinations. This project will create 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 will be the ultimate impact of this project.

Impact on the metrology and scientific communities

This project will create an early impact as it will allow 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 will result in new calibration services for customers. The new traceability chain and primary standards will be validated through an inter-comparison with stable transfer standards, in order to provide new measurement capabilities.

New optical-based calibration methods are being developed, and impact will be created as these methods will be 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 will be drafted to describe the different calibration methods, the conditions under which they must be operated, the target uncertainty and the best working practices. This will be submitted to EURAMET and made available to end users.

Two 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 all the community.

Impact on relevant standards

In this project, procedures and methods for the calibration of drug delivery devices that are already on the market will be developed. The consortium will create impact by supplying this information to the relevant ISO technical committees (TC) and will endeavour 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 of IEC 60601-2-24 (Accuracy of operating data and protection against hazardous output). 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 are following its progress.

Input will be 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.

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 under ISO TC 48/WG4 is now under DIS status. IPQ is following this work. Also, under TC 48/WG5 the new ISO/DIS 23783-1, 2 and 3 are being developed with the contributions from this consortium.

ISO/TC 150/SC 6 has started the revision of ISO14708-4 and the consortium has sent comments to the document.

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

AAMI TIR101 - Fluid delivery performance testing for infusion pumps is under revision and our consortium was invited to supply comments on the document. This document is almost finalised.

Longer-term economic, social and environmental impacts

This project will directly benefit society because it will allow dosing errors, in the drug delivery devices that are used for patient treatment and diagnostics, to be identified and reduced.

Improvements in the instruments' accuracy will reduce dosing errors, thus lives will be saved. This will be achieved through the wider uptake of traceable calibrations of low and ultra-low flow infusion (master) devices and by improved knowledge of how to calibrate drug delivery devices in clinical environments, especially in the case of multiple infusion systems.

List of publications

- 1) "Method selection to evaluate measurement uncertainty in microflow applications" published in *Journal of Physics* <https://iopscience.iop.org/article/10.1088/1742-6596/1379/1/012033>
<https://iopscience.iop.org/article/10.1088/1742-6596/1379/1/012033>
- 2) "Calibration of Insulin Pumps" published in *Journal of Diabetes and Treatment* http://www.drugmetrology.com/wp-content/uploads/2020/02/1575449809article_pdf938882132.pdf
<https://doi.org/10.1088/1742-6596/1379/1/012033>

- 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>

This list is also available here: <https://www.euramet.org/repository/research-publications-repository-link/>

Project start date and duration:		1 June 2019, 36 months
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Internal Funded Partners:	External Funded Partners:	Unfunded Partners:
<ol style="list-style-type: none"> 1. IPQ, Portugal 2. CETIAT, France 3. CMI, Czech Republic 4. DTI, Denmark 5. METAS, Switzerland 6. NEL, United Kingdom 7. NQIS, Greece 8. RISE, Sweden 	<ol style="list-style-type: none"> 9. DNV GL, Netherlands 10. HSG-MIT, Germany 11. INESC MN, Portugal 12. THL, Germany 13. UMCU, Netherlands 	<ol style="list-style-type: none"> 14. BHT, Netherlands 15. KRIS, Republic of Korea
RMG: -		