Publishable Summary for 18HLT08 MeDDII
Metrology for Drug Delivery

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.

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.

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).

Progress beyond the state of the art

In 2004, an effort to understand and improve multi-infusion, defined the crucial metrological 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 went 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 developed 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, mainly the front track method, new displacement methods (e.g. interferometry) and the micro PIV method.

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

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, were developed. The new measurement methods are based on optical, interferometry, displacement method (piston prover) and microPIV (Particle Image Velocimetry) technology. It was possible to go down to 5 nL/min with a 2 % uncertainty.

Also, a multi-infusion setup was 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 enabled 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 reflects a more realistic mixing behaviour in the infusion lines and it was 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 development of new or existing methods for the measurement of microflow rates down to 5 nL/min was completed. Descriptions of each technique with the corresponding measurement uncertainties for each partner are available in the report: 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 (available on www.drugmetrology.com and Zenodo).

An interlaboratory comparison has been performed by ten partners in order to validate the developed measurement methods for static and dynamic flow calibration. 90 % of the results were consistent with the reference value. The final report of the project is now published on the EURAMET webpage. Based on the results obtained in this comparison, several partners have now published new CMCs. The measuring range described in the objective for the static measurement was achieved by several partners. Regarding the uncertainty, the values were higher than the ones described due to the method limitations. The highest expanded uncertainty achieved for steady flow rates was of 2 % at the lower flow rate of 5 nL/min. For the fast-changing flow rate it was possible to measure 20 nL/min with 2 % uncertainty. It was possible to characterise infusion device analyses, a syringe pump and an insulin pump and two different flow sensors.

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.

Three NMI's (RISE, NEL and METAS) developed their micro pipe viscometer for the in-line measurement of dynamic viscosity at micro flow rates. Validation measurements with eight liquids such as saline solutions, glucose solutions (various concentrations) and mixtures of saline and glucose solutions as well as glycerol-water mixtures have been performed in the technical comparison, where three pipe viscometers, three

glass capillary viscometers (widely used as primary standards for the measurement of kinematic viscosity) or rotational viscometers were used. The stated uncertainties of the pipe viscometers, which are smaller or equal to 2 % (k=2), have been validated. The description of the pipe viscometers and the results of the technical comparison were reported in the “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)” (available on www.drugmetrology.com and Zenodo).

The commercially available in-line sensor VLO-M1 from Truedyne Sensors AG for density and dynamic viscosity has been characterised with the eight liquids in order to confirm the stated accuracy. Measurements with the multi-parameter sensor (technology demonstrator) of Bronkhorst High-Tech B.V. were performed with some of the eight liquids. All of the results are reported in the “Report on the use of a calibrated microfluidic multi-parameter chip for the in-line measurement of pressure, viscosity and temperature” (available on www.drugmetrology.com and Zenodo). Therefore, this objective was totally achieved in terms of the target uncertainty and the measurements results and capabilities developed.

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.

A protocol for testing and defining calibration procedures for the drug delivery devices was developed. The measurements with an insulin pump, an implantable pain pump, a syringe pump as well as an infusion device analyser (IDA) have been performed and the results have been analysed and discussed in the report - Characterisation 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 published on (available on www.drugmetrology.com and Zenodo). A EURAMET guideline on the calibration of drug delivery devices was developed as a "EURAMET guideline on the calibration of existing medical drug delivery devices (e.g. insulin pumps, pain controllers and peristaltic pumps) with traceability to a primary standard and with a target uncertainty value of 2 % (k=2) between 5 nL/min and 600 mL/min". This document has been assigned to the EURAMET TC-F Liquid flow subgroup, which is responsible for the publication.

A microfluidic pump has been developed and fabricated, which was reported as the “design document for a new mechanically active on-chip flow pump that will be integrated in a microfluidic device for use as a transfer standard in drug delivery and in organ on a chip applications for flow rates lower than 100 nL/min” (available on www.drugmetrology.com and Zenodo). The two main activities of this objective were achieved as proposed initially by the partners.

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.

To compile a list of components of a clinically representative multi-infusion system, a survey based on a questionnaire and face-to-face interviews was performed. Thus, a test matrix has been defined for the characterisation of components of multi-infusion systems and several clinically representative multi-infusion systems, which were built at THL and UMCU for characterisation measurements. Additional measurements, of the flow resistance and the mechanical compliance of the components, have been performed at NEL and METAS. A clinically representative multi-infusion system has also been characterised at NEL for the validation of the extended predictive model of multi-infusion. The validation results of these measurements as well as the effect of check valves and air bubbles in infusion lines were reported in the "Validation report on the extended prediction model for multi-infusions" (available on www.drugmetrology.com and Zenodo).

Based on the responses to the survey and the characterisation of the clinically representative multi-infusion systems 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 and fluids with different viscosities, including guidance on check valves and other components that benchmark stability in flow rates" has been developed (available on www.drugmetrology.com and Zenodo). This objective provided the necessary tools to go forward in this

cooperative direction to develop conditions for safe drug delivery even with some setbacks due to the covid 19 pandemic, therefore it was achieved.

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.

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

10) Development of an experimental setup for micro flow measurement using the front tracking method, Measurement: Sensors, 18, 100152, https://doi.org/10.1016/j.measen.2021.100152

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

12) Application of the front tracking method in micro flow measuring devices, Measurement: Sensors 23 (2022) 100397 https://doi.org/10.1016/j.measen.2022.100397

13) Predictive performance of pharmacokinetic models for target concentration-controlled infusion of cefoxitin as a prophylactic antibiotic in patients with colorectal surgery, CEPP, Volume 49, Issue 10, https://DOI: 10.1111/1440-1681.13695

14) 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

15) Development of infrared absorption-based flow sensor for in-situ measurement of dispenser discharge amount, Optics and Lasers in Engineering, Volume 161, 2023, https://doi.org/10.1016/j.optlaseng.2022.107334

16) "Metrology in health: challenges and solutions in infusion therapy and diagnostics" Biomedical Engineering / Biomedizinische Technik, 2022. https://doi.org/10.1515/bmt-2022-0045

17) "Measurement of internal diameters of capillaries and glass syringes using gravimetric and optical methods for microflow applications" Biomedical Engineering / Biomedizinische Technik, 2022. https://doi.org/10.1515/bmt-2022-0033

18) “In-line measurements of the physical and thermodynamic properties of single and multicomponent liquids” Biomedical Engineering / Biomedizinische Technik, 2022. https://doi.org/10.1515/bmt-2022-0039

19) "Calibration of insulin pumps based on discrete doses at given cycle times" Biomedical Engineering / Biomedizinische Technik, 2022. https://doi.org/10.1515/bmt-2022-0040

20) "Calibration methods for flow rates down to 5 nL/min and validation methodology" Biomedical Engineering / Biomedizinische Technik, 2022. https://doi.org/10.1515/bmt-2022-0049

21) “Assessment of drug delivery devices working at microflow rates” Biomedical Engineering / Biomedizinische Technik, 2022. https://doi.org/10.1515/bmt-2022-0053

22) "Holographic PIV/PTV for nano flow rates–A study in the 70 to 200 nL/min range" Biomedical Engineering / Biomedizinische Technik, 2022. https://doi.org/10.1515/bmt-2022-0055

23) “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

24) “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

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