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. 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 thus to 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 widespread application in critical health care, infusion errors are often made, with reported dramatic effects in different applications in the health sector, especially in neonatology. There are various examples where adverse incidents, morbidity and mortality, can be traced back to poor inaccurate dosing.

EMRP JRP HLT07 MeDD found that drug delivery devices play a critical role in the safety of patients and a review, in which the medical errors associated with flow rate variability in drug delivery devices, has been published. These errors may result in serious health consequences for the patient including severe health damage or death.

Although patient monitoring gives an indication of possible dosing errors, which results in an adjustment of the flow rate, in multi-infusion applications the actual dosing conditions, beyond the mixing point in the infusion line, is 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. Therefore, 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, and this will enable users to have better metrological knowledge of these devices, preventing incorrect measurement results and thus significantly improving patient safety and saving human lives.

Metrology is needed to bridge the knowledge gap by designing a representative multi-infusion system to test how different liquids mix and how this affects drug concentration. Also the increasing implementations of novel microfluidic solutions in healthcare 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 and results

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 the drugs that are 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.

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.

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.

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.

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, based on flow rate and pressure drop. These investigations will help to prevent dose fluctuations and they will improve occlusion alarm reliability.

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.

Furthermore, novel flow and volume measurement methods and calibration procedures for existing drug delivery devices (e.g. insulin pumps or pain pumps), organ-on-a-chip devices and in-line sensors operating at very low flow rates, i.e. < 100 nL/min, will be developed.

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.

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.

Impact

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.

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 will be developed and impact will be created as these methods will be disseminated to the scientific community in relevant publications. 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 have to be operated, the target uncertainty and the best working practices. This will be submitted to EURAMET and made available to end users.

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 endeavor 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).

The aforementioned standard is going into revision in 2020. The timing of this project is therefore advantageous because the knowledge generated will be directly used by the TCs to start amending the standard.

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.

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.

Project start date and duration:	1 June 2019, 36 months	
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