Final Publishable JRP Summary for HLT07 MeDD
Metrology for drug delivery

Overview

Dosing errors in drug delivery can result in adverse patient incidents, for example dangerous under and overshoot of blood pressure in pre-term newborns. The project focused on developing and using metrological tools to characterise complete drug delivery systems for drug administration by means of infusion technology. At the start of the project these metrological tools were underdeveloped in Europe. Furthermore, the lack of metrology infrastructure was not sufficiently recognised, leading to unawareness of dosing errors, potentially leading to adverse incidents in patient treatment. The metrological tools developed in this project, together with a greater awareness on the causes and impact of dosing errors are now available for the health care community, ultimately leading to a reduced number of dosing errors.

Need

Drug delivery is the process of administering a pharmaceutical compound to achieve a therapeutic effect. Drug delivery by infusion therapy deals with all aspects of fluid and medication infusion, usually via the intravenous route (infusion directly into a vein). For certain medication schedules (e.g. drugs that are only therapeutically active over short timescales or within a narrow range of delivered concentrations or drugs that require a very small blood concentration) the actual flow rate of the infusion equipment is important to ensure the delivery of known quantities of a drug for safe and efficient patient treatment.

Drug delivery by infusion is being given much attention by the health care community because recent studies have identified underestimated risks. Adverse incidents in patients' treatment are believed to be caused by i) poor understanding of the performance characteristics of the complete drug delivery system, ii) under developed metrological infrastructure and iii) lack of awareness of the impact of the potential dosing error.

The characteristics of a drug delivery system (ie start-up behaviour, flow rate error and stability, and potential dependency on physical and environmental parameters) follow from the pump type and disposables used. The metrological infrastructure involves procedures and equipment such as flow meters and high-end syringe pumps and the establishment of primary and secondary standards that allow the performance of clinical measurement components and systems to calibrated ensuring they are accurate when used in practice.

In addition, for low flow rates, lower than 100 ml/h, the existing metrological infrastructure had not been validated and characterised, and for ultra-low flow rates, lower than 0.5 ml/h, the infrastructure did not exist before this project. This meant that drug delivery involving low and ultra-low flow rates could not be measured traceably, which posed a risk in achieving the required accuracy (for critical drug delivery typically 5% accuracy is requested on the dosing rate).

The lack of the required metrological infrastructure (i.e. primary and secondary standards) and the poor understanding of the characteristics of drug delivery systems poses risks in drug delivery and must be addressed.

Scientific and technical objectives

In response to this problem, this project set out to develop the metrology infrastructure that is required by the healthcare community and to carry out performance tests on different drug delivery devices.

The key scientific and technical objectives were the:

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European Metrology Research Programme
Programme of EURAMET

The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union

- Development and characterisation of primary standards for liquid flow at atmospheric conditions for flow rates from 600 ml/h down to 60 nl/h with a target uncertainty better than 0.5 %.
- Characterisation of commercially available flow meters. The focus was on pulsation; however the influence of various physical parameters and connectors were also investigated.
- Metrological assessment and characterisation of drug delivery systems. This included the delivery systems as well as the tubing and needles to actually deliver the drugs.

Results

Development and characterisation of primary standards
In order to realise the required metrological infrastructure, several primary standards for liquid flow have been developed. These standards are based on the gravimetric principle, front-tracking of a meniscus in a capillary or volume expansion and enable flow rate calibrations down to 300 nl/h for the first time. The gravimetric standards use different principles to minimise, or correct for, evaporation. Intercomparisons, based on several flow meters and a syringe pump, were designed to study the consistency of the primary standards. They revealed that all standards are consistent with each other within the claimed uncertainties for a flow range of 3 µl/h to 600 ml/h (except for one lab for the largest flow point). Following these intercomparisons, three project partners (VSL, METAS and IPQ) have claimed Calibration and Measurement Capability (CMC) entries at either the BIPM or country-specific accreditation. The uncertainties obtained ranged from 0.7% for the lowest flow rate to 0.1% for the highest flow rate.

Assessment of flow meters
The primary standards for liquid flow have been used to characterise several commercially available flow meters. The results revealed that the metering accuracy is not significantly affected, with respect to the claimed accuracy, by the operating conditions such as temperature, back pressure and viscosity. Therefore, existing micro flow meters can be used to assist the healthcare community in the realisation of the required level of accuracy of their infusion equipment. Furthermore, existing micro flow meters can be used for varying process conditions and ranges of fluids (viscosities up to 4 times that of water did not show a significant impact on mass based flow meters). The results may also be beneficial in different application fields such as semiconductor processing, fuel cell technology, food, chemical and pharmaceutical industries.

Because the capillaries and tubing used in the microfluidic applications have very small dimensions, a fully developed laminar flow is a very good assumption. Consequently, for the same flow rate, despite potentially different fluid properties, one will find a very similar velocity profile. This is an advantage since this profile can affect the flow meter. This was confirmed by numerical simulations as well as measurements from micro Particle Image Velocimetry.

Assessment of drug delivery systems
The primary standards have also been used to characterise several complete drug delivery systems (infusion pump and one or more accessories, e.g. filters, check valves and varying infusion lines). The results revealed that the performance of the total system greatly depends on the syringe volume, infusion line length and filling procedure of the syringe. Furthermore, it was found that the infusion rate was not significantly affected by the viscosity and back pressure (for a pump without accessories). Typically, the infusion devices operate within specifications, however for large syringes (50 ml) and very low flow rates (lower than 2 ml/h) there was more variance in the results and the measured error was not always within the claimed specifications of the components. The knowledge and experience have been collated in a best practice guide which can help the users of infusion technology to get a better understanding of the causes of dosing errors and ways to minimise or even avoid them.

Actual and potential impact

Dissemination
The project outputs have been shared widely with the metrology, instrumentation and clinical communities. The project has resulted in 10 peer-reviewed publications, 43 presentations or conference proceedings. E-learning material for creating awareness on physical aspects of multi-pump infusion has been developed. 6

technical reports and one good practice guide have been written. These documents can be downloaded from the project website www.drugmetrology.com or the EURAMET repository. A special issue of the Journal of Biomedical Engineering was published and contains many results from this project.

The good practice guide describes what can cause dosing errors, when to expect them and how they can be avoided or circumvented. This guide is tailored at clinical users and it is hoped it will facilitate a reduction of dosing errors. Various hospitals (mainly Dutch and Portuguese) have shown an interest in using it to educate their staff. In addition, other organisations such as the European Society for Intensive Care Medicine, have shown an interest in an e-learning module based on this best practice guide. This e-learning module is available to all ESICM members to offer additional training on the risks of infusion technology.

A project workshop in 2013 at METAS in Switzerland attracted the most important manufacturers of micro flow meters. Two 1-day conferences have been organised by the project in 2014 (Lübeck, Germany) and 2015 (UMC Utrecht, Netherlands). For both conferences roughly 80 delegates participated who represented the medical sector, academia, industry and the metrology sector.

The knowledge gained in the project has been integrated in existing metrology training courses provided by METAS, UMC and VSL to professionals in flow metrology. In addition technical consultancy has been given to third parties as well as other National Metrology Institutes (NMIs) in Europe and Asia to help them in realising and/ or validating primary standards for microfluidic calibrations.

Early impacts

Following the intercomparisons of the primary standards carried out in this project, three project partners (VSL, METAS and IPQ) have claimed CMC entries at either the BIPM or country-specific accreditation board, and two other partners (DTI and CETIAT) could provide evidence for their existing claim. This is an important part of the international system of quality assurance of primary standards held at NMIs. Furthermore, the intercomparisons conducted in the project have enabled the project collaborators VTT and Bronhorst High-Tech to validate their uncertainty budget which enables them to get accreditation for their calibration services too. Finally, several NMIs outside Europe have shown interest in carrying out low flow rate intercomparison(s) to validate their facilities.

The metrological infrastructure developed in this project is now fully in place and the new calibration capabilities are being used. International flow meter manufacturers and NMIs have shown an interest in the services to calibrate their facilities or to help validate their calibration, and the number of requests for calibration services are increasing.

The metrological infrastructure developed in this project enables hospitals to perform high quality checks on infusion pumps. So far two hospitals in Europe have used the derived-standards realised in this project to perform a cross check on their in-house reference meters. It also enables hospitals to check whether a certain combination of infusion pump and disposable equipment yields an acceptable dosing accuracy. This is important because the combination of disposables and equipment from various manufacturers is prone to dosing errors. For those cases, existing master calibrators can directly be used to investigate whether the combination does or does not result in dosing errors.

Drug delivery by infusion is necessary to deliver e.g. anaesthetics, insulin and vasoactive drugs to millions of patients every year. Wider uptake of traceable calibrations of low and ultra-low flow infusion (master) devices and improved knowledge of calibrating infusion equipment in clinical environments will lead, over time, to reduced errors in precision drug delivery. Reduced dosing errors will reduce the number of adverse incidents in patients' treatment. Hence, ultimately, the project in the long term will improve the robustness and reliability of drug delivery and support the delivery of better healthcare.

Finally, the metrological infrastructure developed in this project may have benefits for the microfluidics sector, such as lab-on-a-chip, high performance liquid chromatography or process industry; because developers of microfluidics products and applications have now an independent and reliable check on the quality of their products.

List of publications

Peer reviewed publications

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Proceedings

1. E. Batista, J. Gala, L. Ribeiro, N. Almeida, E. Filipe, R. F. Martins, Development of a microflow primary standard, 5th National meeting of the Portuguese Society of Metrology
2. E. Batista, N. Almeida, E. Filipe, A. Costa, Calibration and use of syringe pumps, II Meeting - Metrology in health
3. E. Batista, E. Filipe, A. Bandeira, H. Navas, Improvement of the microflow primary gravimetric standard, 4th meeting of Portuguese quality researchers
4. E. Batista, J. Gala, L. Ribeiro, N. Almeida, E. Filipe, R. F. Martins, Development of a microflow primary standard, FLOMEKO, Paris, 2013
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JRP start date and duration:	1 June 2012, 36 months
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The EMRP is jointly funded by the EMRP participating countries within EURAMET and the European Union