

## **Title: Metrology for drug delivery**

### **Abstract**

Drug delivery devices and multi infusion systems, which deliver liquids at very low flow rates, < 100 nl/min, and volumes are in widespread use. However, these systems sometimes fail, or deliver the wrong amount of active substance, resulting in dosage errors and adverse effects on patients. A metrological approach is needed to improve patient treatment and safety. Improved calibration procedures are needed for infusion device analysers and the information needs to be incorporated into relevant standards in order to improve error identification in the infusion pumps installed in hospitals. This will increase measurement accuracy and precision. In addition, the behaviour of medication mixtures, fast changing flow rates and drug concentrations in drug delivery needs to be elucidated, as do the effects on the patients, during single or multiple IV infusions. These metrological developments will enable hospitals to deliver drugs more reliably and safely to patients.

### **Keywords**

Microflow, nanoflow, drug delivery, flow sensors, traceability, infusion pumps, pain control pumps, infusion pump analysers, multi infusion systems

### **Background to the Metrological Challenges**

The previous EMRP JRP HLT07 MeDD focused on developing a primary standard for flow rates down to 100 nl/min, on the characterisation of flow meters and flow generators, and on the validation of infusion pumps. The outcomes were disseminated in EMPIR SIP 15SIP03 InfusionUptake and this included revision of two standards: ISO 7886 and IEC 60601-2-24. This SRT focuses on resolving the dosing errors associated with infusion devices and multi infusion systems.

Infusion-based delivery is used to deliver anaesthetics, insulin, vasoactive drugs etc. to millions of patients every year. However, drug delivery systems are prone to errors, and the flow rate and the proportion of each drug being administered cannot be accurately determined in multi infusion systems. To address this, there needs to be wider uptake of the traceable calibration of low and ultra-low flow master devices for infusion. In addition, there needs to be improved knowledge of how to calibrate infusion equipment. Flow facilities also need to be upgraded to allow the very small volumes that are administered, at a given time interval, by insulin or pain pumps (specifically intrathecal drug pumps), to be traceably determined and calibrated to avoid any systematic error from pressure effects in the infusion lines. Recent studies have shown the promise of capacitive droplets sensors, quartz crystal microbalances and air flow sensors as very elegant, accurate and cost efficient measurement methods that could be integrated into liquid handling instruments for on-site re-calibration and verification.

New traceable techniques need to be developed for generating and measuring fast changing flow rates, under 100 nl/min, within seconds in order to enable the different response times of infusion devices and flow sensors to be characterised and validated for the accurate measurement of the volumes administered.

Currently, existing flow facilities are only suitable for use in the characterisation of single flow components. These facilities need to be upgraded to enable multi infusion systems, which comprise several 'standalone' infusion lines and drug delivery devices, to be characterised. Sensors, which can measure multiple parameters (flow, pressure and viscosity) need to be installed along the infusion lines to enable the traceable inline measurement of the average viscosity of non-Newtonian liquids as a function of flow rate and pressure. These sensors feed information back to a controller to enable drug delivery to either be adjusted in a timely manner or an alarm set. The measurement uncertainties will need to be validated and this can be undertaken using Newtonian liquids if the viscosity can be traceably measured using other methods. New measurement procedures are also needed for the traceable measurement of non-Newtonian liquids/multi-phase fluids.

Hospitals need better validated calibration procedures for their existing medical flow devices (e.g. infusion pumps, pain controllers and infusion pump analysers) that operate at very low flow rates, i.e. < 100 nl/min, and the performance of these devices needs to be monitored to ensure that results are reliable. A metrology infrastructure is necessary to ensure that each hospital maintains traceability to a primary reference otherwise results cannot be compared between hospitals.

The drug flow delivered by multi infusion systems is not currently measured at the mixing point in the infusion line. This situation is further complicated in intravenous (IV) infusion by the following factors, which can result in flow-rate variability in the pre-set flow: the types infusion devices used, the internal volume of the IV delivery system, the total compliance of the IV administration set, the presence or absence of valves and/or filters on the main infusion line, and the size of the common volume in which the drugs are mixed. This all means that the actual flow rate, and the proportion of each drug being administered, cannot be accurately determined. Therefore, the accuracy of drug delivery using multi infusion systems needs to be improved in order to reduce dosing errors and adverse effects on patients. To do this a representative multi infusion IV system needs to be developed with several options for testing how liquids, with different physical properties, mix and flow and how this effects drug concentration. Flow rates and pressures need to be metrologically characterised in all infusion lines, as well as at the outlet of the syringe pump, in order to detect occlusion phenomena and bad mixing configurations.

## Objectives

Proposers should address the objectives stated below, which are based on the PRT submissions. Proposers may identify amendments to the objectives or choose to address a subset of them in order to maximise the overall impact, or address budgetary or scientific / technical constraints, but the reasons for this should be clearly stated in the protocol.

The JRP shall focus on the traceable measurement and characterisation of existing drug delivery devices and multi infusion systems, using mixtures of liquids at very low flow rates and volumes, thus enabling reliable, highly efficient drug delivery to patients.

The specific objectives are

1. To develop new traceable techniques for generating and measuring fast changing flow rates, under 100 nL/min, within seconds. The developed techniques should be used to characterise and validate the different response times of infusion devices and flow sensors and to accurately measure the administered volumes with the required uncertainties.
2. To upgrade existing flow facilities to enable the traceable inline measurement of the average viscosity of non-Newtonian liquids, as a function of flow rate and pressure, with the required uncertainties. The measurement uncertainty should be validated using Newtonian liquids if the viscosity can be traceably measured using other methods. Procedures should also be developed to enable new measurement techniques to be used for the traceable measurement of non-Newtonian liquids/multi-phase fluids.
3. To develop and validate novel calibration procedures for existing medical flow devices (e.g. infusion pumps, pain controllers and infusion pump analysers) operating at very low flow rates, i.e. < 100 nL/min, with traceability to a primary standard and with the required uncertainties.
4. To design a representative multi infusion intravenous (IV) system with several options for testing how liquids, with different physical properties, mix and flow and how this effects drug concentration. The flow rates and pressures should be metrologically characterised in all infusion lines, as well as at the outlet of the syringe pump, in order to be able 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 (accredited laboratories, instrumentation manufacturers), standards developing organisations (ISO/TC 30, ISO TC/SC 62D, ISO/TC 76, ISO/TC 84, ISO TC 150, ISO TC 212) and end users (e.g. hospitals and health centres).

These objectives will require large-scale approaches that are beyond the capabilities of single National Metrology Institutes and Designated Institutes, and it is expected that multidisciplinary teams will be required. To enhance the impact of the research, the involvement of the appropriate user community such as medical practitioners, hospitals and industry is strongly recommended, both prior to and during methodology development.

Proposers should establish the current state of the art, and explain how their proposed project goes beyond this.

In particular, proposers should outline the achievements of the EMRP JRP HLT07 MeDD and EMPIR SIP 15SIP03 InfusionUptake and how their proposal will build on those.

EURAMET expects the average EU Contribution for the selected JRPs in this TP to be 1.8 M€, and has defined an upper limit of 2.1 M€ for this project.

EURAMET also expects the EU Contribution to the external funded partners to not exceed 35 % of the total EU Contribution across all selected projects in this TP.

## Potential Impact

Proposals must demonstrate adequate and appropriate participation/links to the “end user” community, describing how the project partners will engage with relevant communities during the project to facilitate knowledge transfer and accelerate the uptake of project outputs. Evidence of support from the “end user” community (e.g. letters of support) is also encouraged.

You should detail how your JRP results are going to:

- Address the SRT objectives and deliver solutions to the documented needs,
- Feed into the development of urgent documentary standards through appropriate standards bodies,
- Transfer knowledge to the pharmaceutical and medical sectors.

You should detail other impacts of your proposed JRP as specified in the document “Guide 4: Writing Joint Research Projects (JRPs)”

You should also detail how your approach to realising the objectives will further the aim of EMPIR to develop a coherent approach at the European level in the field of metrology and include the best available contributions from across the metrology community. Specifically, the opportunities for:

- improvement of the efficiency of use of available resources to better meet metrological needs and to assure the traceability of national standards
- the metrology capacity of EURAMET Member States whose metrology programmes are at an early stage of development to be increased
- organisations other than NMIs and DIs to be involved in the work

## Time-scale

The project should be of up to 3 years duration.