Publishable JRP Summary Report for JRP HLT07 MeDD Metrology for drug delivery

Background

Drug delivery is the process of administering a pharmaceutical compound to achieve a therapeutic effect. Typically, the amount of drug delivered and the drug itself are the most important parameters. However, there are a significant percentage of drugs for which the actual flow rate is important for a safe and sound patient treatment. This is, in particular, the case for drugs that have a short half-life and a narrow therapeutic band width, or for drugs that require a very small blood concentration for reasons of toxicity. The half-life is the time in which the concentration of a drug in a human is decreased by 50%. A short half-life is in the order of 1 minute.

Currently, infusion technology is given much attention because recent (national) studies have identified that there are underestimated risks involved in drug delivery. This is because there have been examples where adverse incidents, morbidity and/or mortality, are believed to be caused by inadequate administration of drugs. These events can probably be traced back to not fully understood **characteristics** of the complete drug delivery system (including disposable), an under developed **metrological infrastructure** and to a lesser extent a lack of awareness.

The **characteristics** of a drug delivery set up refer to the start-up behaviour, flow rate error and stability, and potential dependency on physical parameters such as the environmental temperature, back pressure and fluid temperature and viscosity. The start up delay of single syringe pumps without any disposables is fairly well known; however the impact of adding disposables (infusion lines, filters, check valves, etc.) is not well known and can be quite significant. Furthermore, the potential impact of temperature, back pressure and viscosity is not well known. Flow rate (and concentration) accuracy can further deteriorate if multi-pump infusion is involved. Multi-pump infusion involves more than 1 pump delivering a certain drug through the same line and injection point. In recent work carried out under MeDD, it was found that a certain neonatal medication schedule using 3 pumps can result in dosing errors up to 10 %, while peak errors could be as high as almost 50 %. Further, start-up delays up to 0.71 ± 0.11 hours were measured.

The **metrological infrastructure** consists of the equipment, procedures and qualified personal to carry out the necessary calibrations and performance tests. For low flow rates, e.g. lower than 100 mL/min, the existing metrological infrastructure has never been validated, whereas for ultra low flow rates, say lower than10 µL/min, the infrastructure does not even exist. Yet, these flow rates are required for certain medication schedules. For example, current medication schedules can require flow rates down to 0.5 mL/h or even 0.1 mL/h (respectively 8.3 µL/min and 1.7 µL/min). Furthermore, highly effective drugs for pain treatment must be administered as a continuous infusion via an intrathecal catheter at starting doses of 70 nL/min. As a result, drug delivery involving low and ultra-low flow rates cannot be traceably measured, which poses a risk in achieving the required accuracy (for critical drug delivery typically 5 % accuracy is requested on the dosing rate).

Need for the project

The lack of the required metrological infrastructure and the incompletely understood characteristics of drug delivery devices pose risks in drug delivery. The goal of this project is therefore to develop the infrastructure that is required by the Health care community and to conduct performance tests for several drug delivery devices.

EMRP European Metrology Research Programme Programme of EURAMET
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The metrological infrastructure will consist of traceable calibration services for drug delivery systems for flow rates down to e.g. 1 ~ 10 nL/min, which is several orders of magnitude lower than the lowest calibration service available in Europe today.

The performance tests of several drug delivery devices focuses on their performance (e.g. start-up time, accuracy, and the flow rate error and stability) and the dependency on operating conditions (e.g. viscosity and temperature). Classic drug delivery devices will be considered, however multi-pump infusion, drug delivery with mobile devices and the influence of drug delivery accessories (such as needles, splitters, valves, tubing, etc.) will also be considered.

Scientific and technical objectives

The work of project HLT07 MeDD is broken down into the following areas:

- Development and characterisation of primary standards for liquid flow at atmospheric conditions for flow rates from 150 µl/min down to 1 nl/min with a target uncertainty better than 0.5 %.
- Characterisation of commercially available flow meters. The focus is on pulsation; however the influence of various physical parameters and connectors will also be investigated.
- Metrological assessment and characterisation of drug delivery systems. This includes both the delivery systems as well as the tubing and needles to actually deliver the drugs.

Expected results and potential impact

Primary standards

In order to realise the required metrological infrastructure several primary standards have been developed. These primary standards rely on different principles so that it is unlikely that all standards lead to same systematic error(s). As a first step, the primary standards of 6 different laboratories participated in an intercomparison for flow rates in the range of 33 µL/min to 10 mL/min (2 laboratories participated as a supplement). This intercomparison revealed that all standards are consistent with each other within the claimed uncertainties (except for the largest flow point). Currently, a second intercomparison is running for flow rates in the range of 50 nL/min to 33 µL/min. Preliminary results show consistency for most flow points. Following these intercomparisons various labs will claim CMC entries at the BIPM or country-specific accreditation board, thereby realizing the required metrological infrastructure.

Other than the health care community, the developed metrological infrastructure can be used by for example research institutes and flow meter manufacturers to facilitate research and development. Other fields are, for example, HPLC (high performance liquid chromatography), lab-on-chip, plant development via down-scaling, and process technology.

Assessment flow meters

Currently, the (validated) primary standards are being used to characterise several commercially available flow meters. First results reveal that the metering accuracy is not much affected by the operating conditions such as the temperature, back pressure and viscosity. This conforms a Poiseuille flow which is defined as a fully developed laminar flow. Because of the very small dimensions of the capillaries and tubing used in the micro fluidic applications and flow meters, a fully developed laminar flow is a very good assumption. Consequently, for the same flow rate, one will have the same velocity profile. In case the viscosity changes (either directly or through temperature), the pressure gradient will have to compensate.

Assessment drug delivery devices

Currently, the (validated) primary standards are being used to characterise several complete drug delivery devices (infusion pump plus one or more accessories). The first results reveal that the compliance greatly depends on the syringe volume, infusion line length and filling procedure of the syringe. Furthermore, it was found that the infusion rate is not significantly affected by the viscosity and back pressure (pump without accessories). Typically, the infusion devices operate within specs, however for large syringes (50 mL) and very low flow rates (lower than e.g. 2 mL/h), there is more variance in the results and the measured error is not always within the claimed specifications. Finally, the start-up delay scales with the compliance and is in

the order of halve a minute to a few minutes. The results from the assessment of drug delivery systems will feed into a best practice guide which can be used by the health care community in using drug delivery devices.

The results obtained in this project have been presented at several conferences and submitted to scientific peer-reviewed journals. Three workshops have been held (Lunteren 2013, Bern 2013, Lübeck 2014) and another one will be organised (Utrecht 2015). The results of MeDD have been presented and discussed at these workshops. A best practice guide will be written to make the results of MeDD available to the health care community. In January 2015 the possibility of a future amendment for one or more written standards used in infusion technology will be discussed with a member of CEN (European Committee for Standardisation).

The JRP website, www.drugmetrology.com, can be accessed for more information or to download technical reports and (conference) papers. In future, training courses will be advertised on general metrology or on metrology specifically relevant for drug delivery.

JRP start date and duration:	1 June 2012, 36 months
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