METROLOGY for DRUG DELIVERY

MEDD II

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2nd Newsletter

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Welcome

One year has passed since the beginning of the project and we welcome you with great pleasure to the second MeDDII newsletter. We take this opportunity to inform and update you about news, achievements and the results of our work. In the first period of the project, the focus was on the development of new traceable techniques for the calibration of drug delivery devices in the measuring range from 5 nL/min to 100 nL/min, using Newtonian liquids. Stakeholder engagement in our project was intensified by establishing an advisory group. A questionnaire for technicians handling simple or multi-infusion setups and for manufacturers of drug delivery devices or components used in simple or multi-infusion setups was completed; 32 responses were received. Four research papers were published in the Journal of Physics and in Flow Measurement & Instrumentation. Also, a case study entitled "*COVID-19 crisis & Emergency Practices with Infusion Pumps in ICU, the role of Metrology"* was published on our website in order to help hospital administrations to develop best practices and guidelines for new emergency COVID-19 drug delivery measures. We hope you will find valuable information in this newsletter. We are keen to keep in contact with stakeholders, users, or anyone generally interested in the work, and we are looking forward to welcoming you into our project community.

Elsa Batista

Coordinator of MeDDII project

News and facts

- A stakeholder advisory group was established with the following members:
  - Erik Koomen, anaesthesiologist and pediatric intensivist on the Pediatric Intensive Care in Wilhelmina Children's Hospital Utrecht in the Netherlands;
  - Morten Kleinstrup, Product Test Competence Manager from Phillips-Medisize A/S from Denmark;
  - Anselmo Costa, head of the Pediatric Intensive Care Unit from Hospital Garcia de Orta in Caparica, Portugal;
  - Stephanie Genay, expert in infusion devices and on the composition of tubing from the University of Lille, France;
  - Robert Butterfield – expert in infusion technology, Biomedical engineer, USA.

- The second project meeting was held at METAS, the National Metrology Institute from Switzerland, in February 2020 (Figure 1).

Figure 1: MeDD II team at METAS: IPQ, CETIAT, CMI, DTI, METAS, NEL, NQIS, RISE, DNV GL, HSG_MIT, INESC MN, THL, UMCU, BHT

• A case study entitled “COVID-19 crisis & Emergency Practices with Infusion Pumps in ICU, The role of Metrology” was published on our website. You can find more information here

• A report on measurement error highlighting the conflicting definitions used in metrology and in medical standards was published on our website. You can find more information here

• The questionnaire for technicians handling simple or multi-infusion setups and for manufacturers of drug delivery devices or components used in simple or multi-infusion setups was completed and 32 responses were obtained. This information will be used to direct the research in WP2, WP3 and WP4.

Highlights from the work packages

During this last year we have been actively engaged in the development of new calibration methods and facilities. This work was mainly done under **WP1 – Development of metrology infrastructure for ultra-low flow rates.**

Different techniques are now under implementation by the different partners, mainly micron resolution Particle Image Velocimetry (micro-PIV), optical, displacement and gravimetric methods (Figure 2). By using different flow generators we were able to achieve a wide range of flow rates with different uncertainty levels: METAS is using a piston prover generating flow down to 20 nL/min with a relative uncertainty of 1 %; DTI is using a gravimetric method down to 16 nL/min with a 4 % relative uncertainty; IPQ developed an interferometric-based method that is able to measure flow rates down to 16 nL/min with a 3 % relative uncertainty; NEL and HSG-MIT are using an optical nanoflow measurement technique based on micro PIV, expected to go down to 1 nL/min; CETIAT and THL have been extending the front track principle down to 1 nL/min, now with a 2.6 % uncertainty.

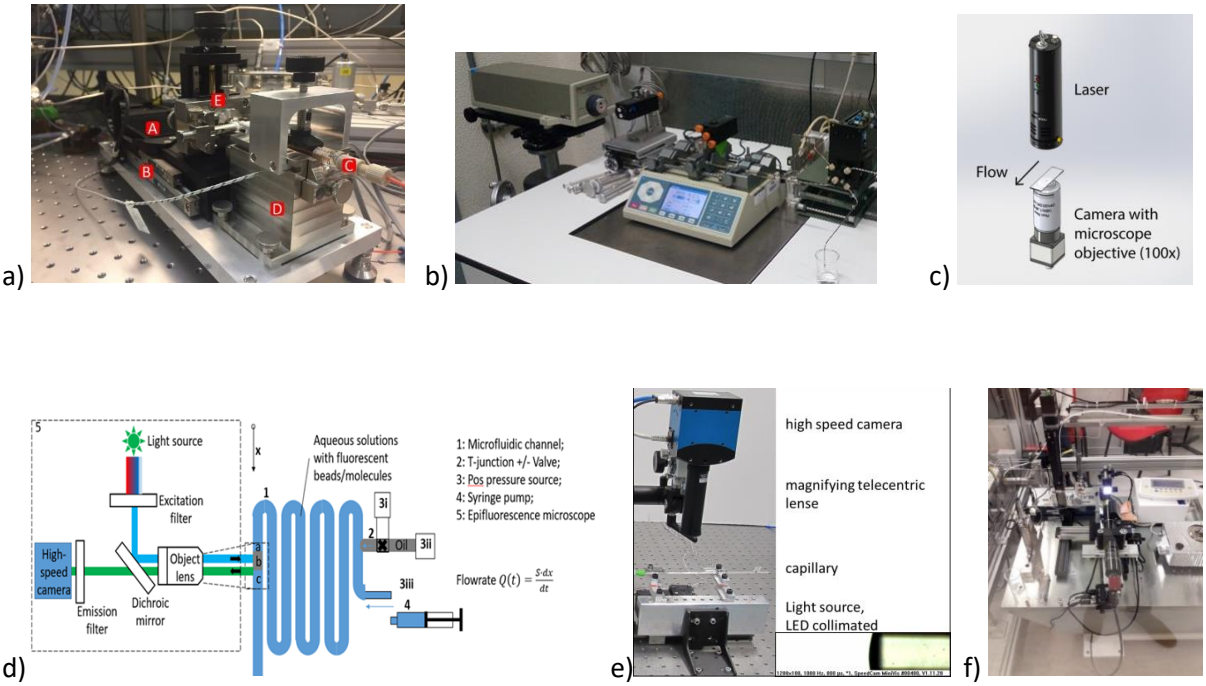

Figure 2: Metrology infrastructures being developed under the scope of MeDD II: a) piston prover at METAS, b) interferometric-based method at IPQ, c) optical nanoflow measurement technique at HSG-MIT, d) optical nanoflow measurement technique at NEL, e) front track principle at CETIAT, f) front track principle at THL

The uncertainty budgets are currently being developed for each method by the different partners.

When the facilities are completed, an interlaboratory comparison will commence to validate the developed measurement methods.

Under **WP 2 – In-line measurement of the physical and thermodynamic proprieties of single and multicomponent liquids**, two questionnaires for clinical users of multi-infusion setups, for technicians using multi-infusion setups and for manufacturers of drug delivery devices were developed and circulated. 33 responses were received and this allowed us to identify the clinically relevant interval for the dynamic viscosities (< 2 mPa s), the flow rates (from 1 μL/min to 10 mL/min) and the liquids to be tested in the next task, namely saline solution, Dopamine and Dobutamine. The clinically relevant pressure interval was also identified, 0.1 bar to 0.5 bar, for occlusion alarms. Several in-line devices have been identified and will be used in the subsequent tasks.

In **WP3 – Development of a microchip pump and calibration procedures**, the relevant types of drug delivery devices and flowrate intervals to be tested have been identified based on the questionnaire response, mainly syringe pumps, infusion device analysers, insulin pumps and pain pumps. It is expected that the performance tests will start in September 2020 and these results will lead to the development of calibration procedures.

The initial diagrams of the microchip flow pump have been produced by INESC MN based on the specifications and they have been used as an input for numerical simulations, which are now concluded. The first physical prototype is expected to be produced by January 2021.

Finally, in **WP 4 – Design and characterization of a multi-infusion system** the clinical best practice guide using multi-infusion systems is under development, based on the answers from the questionnaires returned and the experience of UMC Utrecht.

The multi-infusion setups are under development according to the planned activities to build a setup for use in therapeutic activities. The predictive model of multi-infusion was extended to multiple flows and different viscosities. A second step will be to include the distortion of flow caused by mechanical obstruction due to components or air bubbles in line.

Dissemination of work

MeDDII experts are actively engaged with the impact on standardization namely ISO 8655 and ISO 23783 from ISOTC48, IEC60601-2-24 fromTC62/SC62D/MT23 and TUR 101 from AAMI.

A poster presentation was performed by Patricia A. G. Canane, Susana Cardoso, Vania Silverio, Biodetection and Diagnostics: Matching surface wettability to compatible Lab-on-chip technology, VIII AEICBAS Biomedical Congress, 12-15 March 2020

Four papers were published in several magazines, in open access, mainly:

- J. A. Sousa, E. Batista, O. Pellegrino, A. S. Ribeiro and L. Martins, Method selection to evaluate measurement uncertainty in microflow applications, Journal of Physics: Conference Series, Volume 1379, Number 1 (2019), https://doi.org/10.1088/1742-6596/1379/1/012033
- E. Batista, et al, New EMPIR project – Metrology for Drug Delivery" published in *Flow measurement instrumentation,* 72 (2020) 101716, https://doi.org/10.1016/j.flowmeasinst.2020.101716
- H. Bissig, M. Tschannen, M. de Huu, Traceability of pulsed flow rates consisting of constant delivered volumes at given time interval, *Flow measurement instrumentation*, 73 (2020) 101729, https://doi.org/10.1016/j.flowmeasinst.2020.101729
- F.Ogheard, P.Cassette, A.W.Boudaoud, Development of an optical measurement method for "sampled" micro-volumes and nano-flow rates, 73 (2020), 101746, https://doi.org/10.1016/j.flowmeasinst.2020.101746

A 1-day workshop on metrology for drug delivery is foreseen to be held at CETIAT in November 2020. further information will be provided on the MeDDII webpage (www.drugmetrology.com) as it becomes available.

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