METROLOGY for DRUG DELIVERY

MEDD II

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3rd Newsletter

01 / 2021

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The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

Welcome

2020 has ended after a very difficult year globally due to the Covid 19 pandemic. In the field of science, it presented many new challenges, especially for those scientists engaged in healthcare research, including our MeDDII - Metrology for drug delivery project. A key highlight and contribution from our project was the development of a case study on the impact of Covid 19 on drug infusion practice in hospitals. Our project and this document was recognized as relevant by the European Commission (EC) and is now also available in the EC website. Despite all the restrictions that caused significant difficulties in performing laboratory work and test measurements, the MeDDII consortium achieved the majority of scheduled tasks. To highlight these achievements in such challenging times, I welcome you with great pleasure to our 3rd MeDDII newsletter. We take this opportunity to provide a status update of the project and inform you about news, achievements and the results of our work. In the last six months, the focus was on finalizing the development of new traceable techniques for the calibration of drug delivery devices, from 5 to 100 nL/min, using Newtonian liquids and initiating the validation process of these new techniques. Twoo research papers were published in open access format and four presentation were performed in relevant conferences. Our first delivery milestone of the project was successfully achieved and a workshop on microflow calibration methods was held virtually in November, with five technical presentations. I hope you will find valuable information in this newsletter. We are keen to keep in contact with you as key stakeholders or as someone generally interested in this work and welcome you into our project community.

Elsa Batista

Coordinator of project MeDDII

News and facts

- Our first deliverable was successfully achieved in October 2020: "Report on calibration methods for measuring the response or delay time of drug delivery devices using Newtonian liquids for flow rates from 5 nL/min to 100 nL/min". It is available for download in the project webpage, here.

- The third meeting of the project was held virtually on the 17th of November. All partners involved in the project participated.

Figure 1 - MeDD II team online: IPQ, CETIAT, CMI, DTI, METAS, NEL, NQIS, RISE, KRISS, DNV GL, HSG-IMIT, INESC MN, BHT, THL, UMCU

•A workshop on Microflow Calibration Methods organized by CETIAT was held virtually in November 2020. This workshop had the main objective of presenting the new methods for calibration of micro flow devices, developed within the project activities and the improvements on methods already implemented for microflow device calibration. The presentations prepared by the project partners were the following:

Introduction to project MeDDII	Elsa Batista, IPQ, Portugal
Gravimetric method	Anders Niemann, DTI, Denmark
Optical methods	Florestan Ogheard, CETIAT, France
µPIV methods	Sabrina Kartmann, Hahn-Schickard, Germany
Displacement methods	Hugo Bissig, METAS, Switzerland

The workshop was a great success with 70 participants from all around the world, interactive Q&A discussions and very positive feedback. All the presentations can be found in our project webpage, here.

Highlights from the work packages

During this last year we have been focused on finalizing the development of new calibration methods and facilities, this work was an objective under **WP1 – Development of metrology infrastructure for ultra-low flow rates.** An interlaboratory comparison protocol has been developed and the measurements will start in January 2021. This comparison has the aim of validating the developed measurement methods for static and dynamic tests with 10 partners participating. The transfer standards chosen are the thermal flow meter L01 from Bronkhorst (1500 to 20 nL/min), the thermal

flow meter SLG-0075 (1500 to 20 nL/min) from Sensirion AG, and a Cetoni pump (100 nL to 5 nL/min) (figure 2).

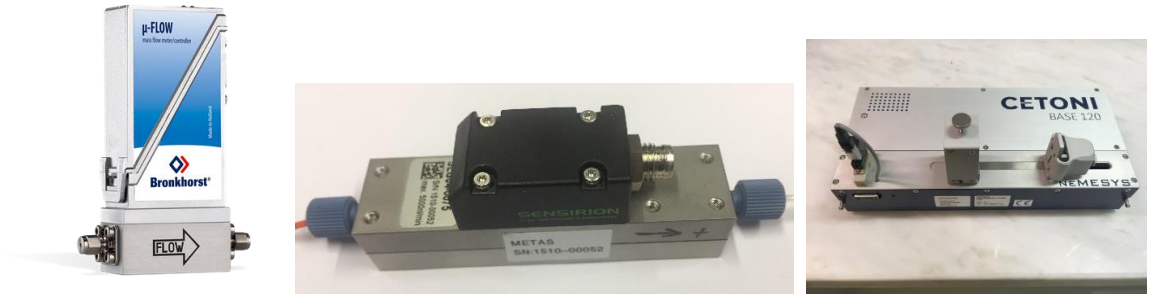

Figure 2 – From left to right, thermal flow meter L01 from Bronkhorst, the thermal flow meter SLG-0075 from Sensirion AG and a Cetoni pump

Under **WP 2 – In-line measurement of the physical and thermodynamic proprieties of single and multicomponent liquids**, the facilities are currently under development and will be validated with reference liquids (traceable density and dynamic viscosity). Validation measurements will be performed with saline solutions and glucose solutions (various concentrations) and mixtures of them. Several in-line devices have been identified and will be used in the subsequent tasks.

In **WP3 – Development of microchip pump and calibration procedures**, from the questionnaire and with inputs from collaborators and stakeholders, the relevant types of drug delivery devices and flowrate intervals have been identified. A protocol for test and defining calibration procedures for the drug delivery devices was developed. The measurements have started in October 2020 and are expected to end in June 2021. The chosen instruments to be tested are an insulin pump, a pain pump, a syringe pump and an infusion pump analyser (figure 3).

Figure 3 – From left to right, insulin pump, a pain pump, a syringe pump and an infusion pump analyser

A design for a micro fluidic pump has been developed and a numerical prototype of the pump has been tested to prove the design by INESC-MN. A physical prototype is under development and construction.

Finally, in **WP 4 – Design and characterization of a multi-infusion system** the list of components required to prepare a clinically realistic setup for multi-infusion drug delivery systems and the test matrix to assess and characterize the typical multi-infusion system are now available.

Multi-infusion setups were built in Lübeck and in Utrecht. The component list and setup were adapted for testing and the sensor integration is currently on schedule. The development of the prototypes has been initiated, as well as the flow cell development.

The predictive model of multi-infusion was extended to multiple flows and different viscosities. Air bubbles and viscosity have been included in the model by UMC Utrecht. To enable the validation of this model Computational Fluid Dynamics (CFD) simulations are under development by NEL. The incorporation of check valves in the model has also started.

Dissemination of work

MeDDII participants are actively engaged with the impact on **standardization** namely ISO 8655 and ISO 23783 from ISO/TC 48, IEC60601-2-24 from TC62/SC62D/MT23, ISO14708-4 from ISO/TC 150/SC 6 and TIR 101 from AAMI.

Four **presentations** were delivered:
1) Oral presentation at the 5th Healthcare & Lifesciences (HLS) workshop, September 2020, Pisa, by Joost Lötters, Bronkhorst High-Tech BV / University of Twente
"*Towards a demonstrator system for real-time in-line measurement of medicine mixtures*"

2) Oral presentation at International Conference on Medical Measurements and Systems 2020 (ICMMS 2020), *Virtual Event,* October 2020 by Elsa Batista, IPQ
"*Calibration of Syringe Pumps Using Interferometry and Optical Methods*"

3) Oral presentation at the International Conference on Medical Measurements and Systems 2020 (ICMMS 2020), *Virtual Event*, October 2020 by Abir Wissam Boudaoud, CETIAT
"Development of a Primary, Portable and Optical System for the Measurement of Nano-flow Rates of Liquids"

4) Oral presentation at *10.º Encontro da Divisão de Química Analítica da SPQ, ANALÍTICA 2020, Virtual Event, Portugal, 26-28 October 2020, by Elsa Batista (IPQ), João Alves e Sousa (IPQ), Susana Cardoso (INESC) and Vânia Silverio (INESC)*
"Flow accuracy and traceability in a Lab-on-a-chip device"

Two **papers** were published in open access peer-reviewed journals:

1) "Development of an experimental setup for microflow measurement using interferometry" published in *Flow Measurement and Instrumentation*
https://doi.org/10.1016/j.flowmeasinst.2020.101789
2) "Calibration of Syringe Pumps Using Interferometry and Optical Methods" published in the *International Journal of Biomedical and Biological Engineering*
https://publications.waset.org/10011517/pdf

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