METROLOGY for DRUG DELIVERY

MEDD II
Drugmetrology.com

Introduction to project MeDD II - Metrology for drug delivery II

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Resume

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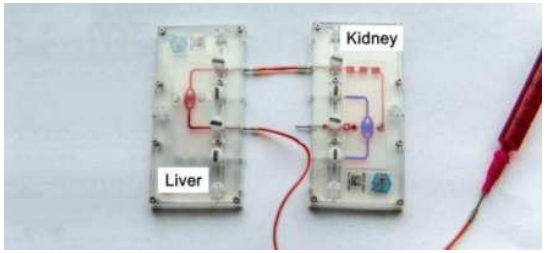

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EMPIR – MeDDII – 18HLT08

Call: 2018 Health

JRP name: Metrology for drug delivery

JRP reference: 18HLT08 MeDDII

Total budget: ~ 1,7 M€

Total labour: ~200 MM

Duration: 36 months

Start date: June 2019

Coordinating Organisation: IPQ

Scientific leader: METAS

Partners - 9 NMIs/DIs, 4 universities, 2 manufacturers. 11 countries

Colaborators - 41

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EMPIR – MeDDII – Team

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Consortium

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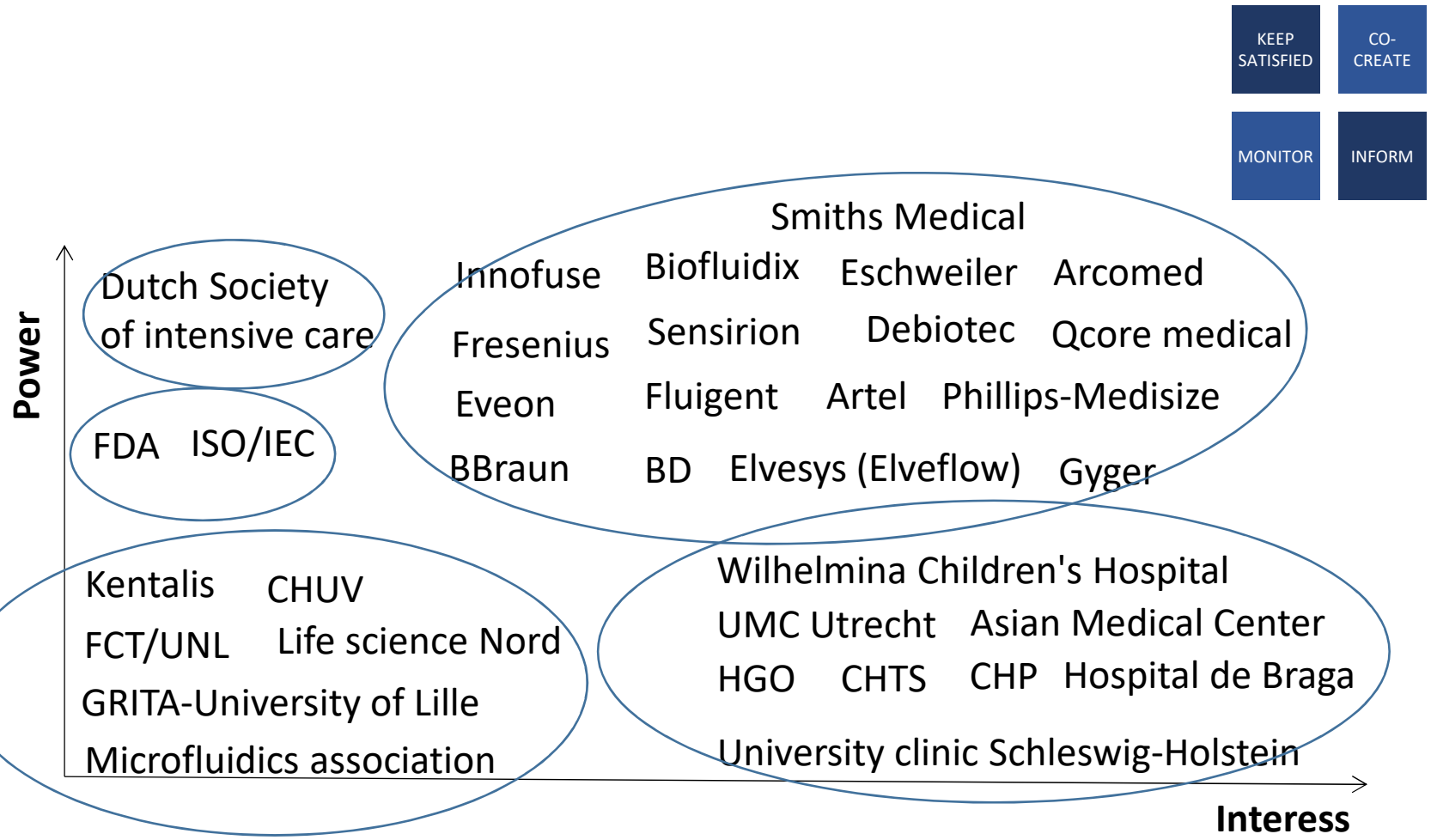
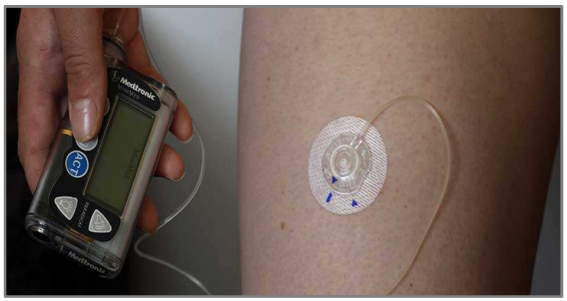
Stakeholder map



Overview

This project aims to characterize and improve dosing accuracy of existing drug delivery devices and multi infusion systems and enable traceable measurements of their volume, flow rate, pressure and inline sensing operation at very low infusion rates:

- ✓ by the development of **new calibration methods**
- ✓ by **expanding the existing metrological infrastructure**



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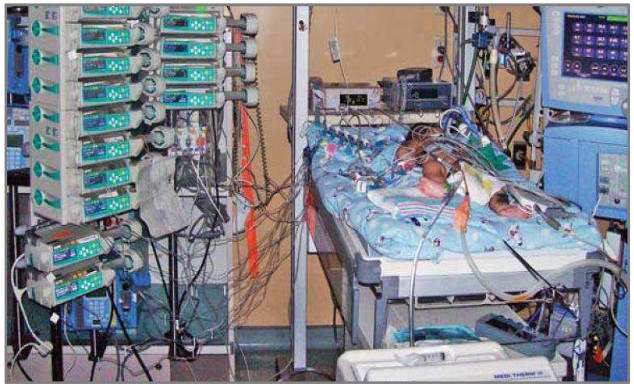
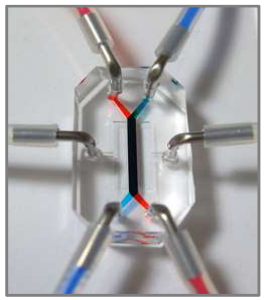
Overview

Additionally this project will investigate:

- the effects of **fast transient flows** on dosing response
- the **physical properties** of liquid mixtures used in infusion
- the **occlusion phenomena** in multi-infusion systems
- development of a new micropump





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Needs and motivation

- **Infusion therapy** → Main form of therapy in health care.
- **Deviations** in medication dose into the patient bloodstream have **dramatic effects.**
- Wide range of applications (vasoactive drugs, multi-infusion therapy, pre-term babies therapy, organ-on-a-chip technology, etc.).

Validated metrological infrastructure for traceable measurement and calibration

- volume
- ultra-low flow rates (< 100 $nL.min^{-1}$)
- pressure
- fast changing flow rate
- physical properties of mixtures
- occlusion phenomena

Crucial for patient safety and to advances in:

- ✓ microfluidics and organ-on-a-chip faithfull reproduction of multi-organ functions
- ✓ reproducibility and accuracy of multi-infusion therapies
- ✓ reliability of drug delivery devices

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Work Packages

WP1 OBJECTIVE 1

Development of metrology infrastructure for ultra-low flow rates

National Engineering Laboratory

- Upgrade existing flow facilities and/or develop new techniques for measurement of **flow rates down to 5 nL.min^{-1}** for steady and fast transient flows.
- Establish robust and realistic **uncertainty budgets**. Target uncertainties at 1 % (k = 2) for steady flows and 2 % (k = 2) for fast transient flows.
- **Validate primary standards**, needed for the characterization of drug delivery devices and multi infusion systems.

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Work Packages

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WP2 OBJECTIVE 2

METAS

In-line measurement of physical and thermodynamic properties

- Upgrade the existing flow facilities of the participant NMIs in order to enable **traceable inline measurement** of the dynamic viscosity of Newtonian liquids, as a function of the flow rate and pressure difference, with a target uncertainty value of 2 % (*k*=2).

- Characterize flow devices for in-line measurements of **physical and thermodynamic properties**. These properties are needed to determine the proportion of components of a mixture of liquids.

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Work Packages

WP3 OBJECTIVE 3

Development of a microchip pump and new calibration procedures of existing medical devices

DANISH TECHNOLOGICAL INSTITUTE

- **Identify the metrology infrastructure** for drug delivery devices and multi infusion systems.
- Develop and validate **calibration procedures** for drug delivery devices and on-chip flow micropump demonstrator.
- Fabricate and characterize a novel on-chip flow micropump as a **transfer standard.**

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Work Packages

WP4 OBJECTIVE 4

Design and characterization of a multi-infusion system

UMC Utrecht

- Develop **multi-infusion setups** to investigate mixing and drug concentration at the patient's point of medication entry.
- Extend and validate a **predictive model** for multi-infusions.
- Develop a **Best Practice Guide** providing methodologies to build/assemble/use multi-infusion set-ups to guarantee the most effective dosing of drugs and fluids to the patient.

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Work Packages

WP5 - IMPACT

New guidance documents

- Draft **new calibration procedures and guides** of drug delivery devices and multi infusion systems

Input for the revision of reference documents

- Promote **Knowledge transfer and exchange** with International Standards Committees.
  - ISO 60601-2-24
  - ISO 7886-2
  - New OIML documents
  - ISO 8655-9

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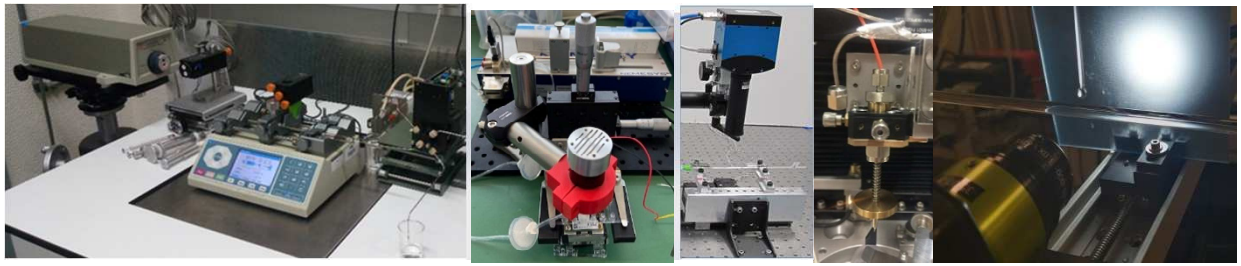
WP1

Development of metrology infrastructure for ultra-low flow rates

- Comprehensive report produced on the new calibration methods for steady and dynamic flow rates
  - A1.2.5 “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”
  - 78-page report provides detailed information on each technique and the uncertainty calculations
  - report freely available on the MeDD II website for download - D1

www.drugmetrology.com/the-first-deliverable-of-project-medd-ii-is-now-available/



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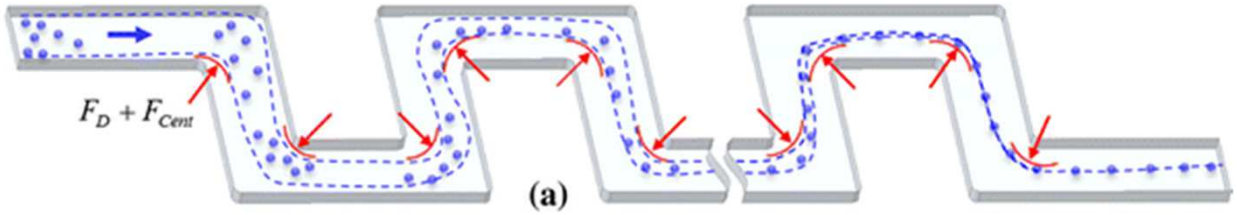
WP1

Development of metrology infrastructure for ultra-low flow rates

- Intercomparison exercise to validate the new techniques & uncertainties will start in Jan 2021



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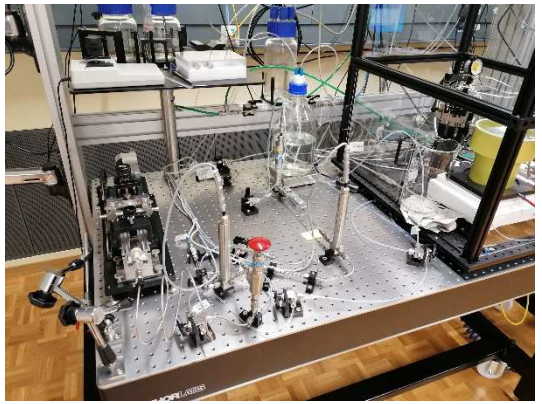
WP2

In-line measurement of physical and thermodynamic properties

❑ **Task 2.1 in-line measurement of dynamic viscosity**

- ***Questionnaire to identify clinically relevant ranges:***
  - ➢ flow rates 1 µL/min – 10 mL/min
  - ➢ pressure range 0.1 bar – 0.5 bar
  - ➢ viscosities 1 mPa*s – 2 mPa*s



- ***Development of primary standards for in-line measurements of dynamic viscosities.***
  - ➢ The facilities are currently under development and will be validated with reference liquids (traceable density and dynamic viscosity). Validation measurements with saline solutions and glucose solutions (various concentrations) and mixtures of them.

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WP2

In-line measurement of physical and thermodynamic properties

- **Task 2.2 In-line measurement for pressure**
- **Task 2.3 Characterisation of devices for in-line measurement of dynamic viscosity**
  - This task will start after the validation of the facilities for the in-line measurement of dynamic viscosities

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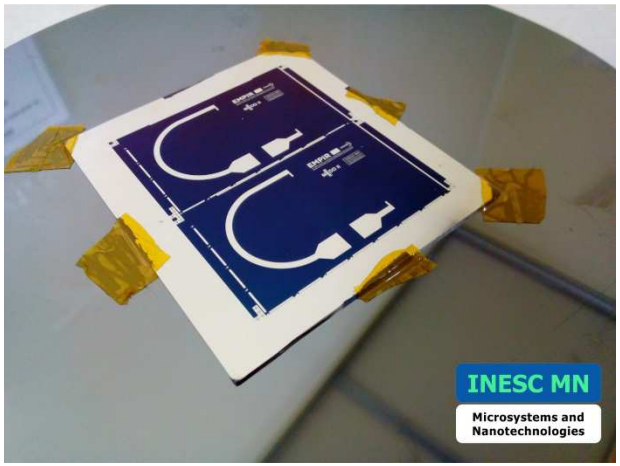
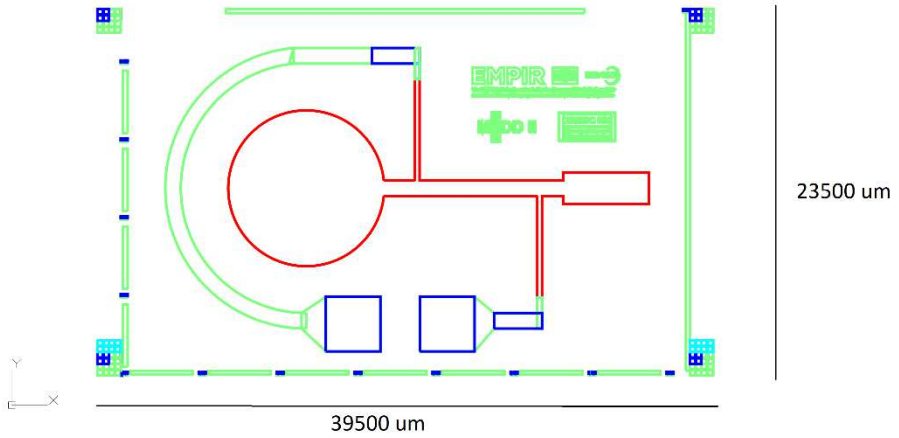
WP3

Development of a microchip pump and calibration procedures

- **3.1: Identification of existing metrology infrastructure for drug delivery devices**
  A survey/questionnaire has been circulated to medical departments and commercial companies.

- **3.2: Development and characterisation of a prototype microchip flow pump**
  A design for a micro fluidic pump has been developed and a numerical prototype of the pump has been tested to prove the design. A physical prototype is under development and construction.

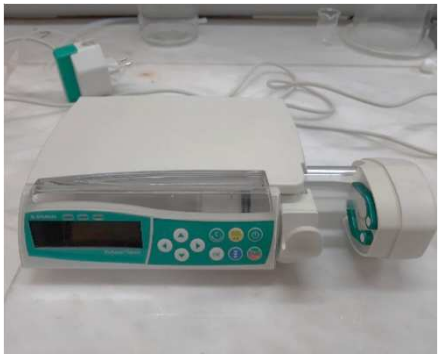




WP3

Development of a microchip pump and calibration procedures

- **3.3: Development of calibration procedures for drug delivery devices and the microchip flow pump**
  A test protocol in order to test the 4 devices selected in task 3.1 has been created based on the responses of the survey. A schedule to circulate the devices between the participating laboratories has been completed and the testing of the devices has been initiated.



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WP4

Design and characterization of a multi-infusion system

- 4.1 - Develop **multi-infusion setups**: Questionnaires have been completed, and the consortium has agreed on a list of components and a test matrix.
  4.2 - Muti-infusion setups were built in Lübeck and in Utrecht. The component list was adapted. The setup record was adapted accordingly. Sensor integration is now on schedule. The work on prototypes started, as well as the flow cell development.

- 4.3 - Extend and validate a **predictive model** for multi-infusions:
  Air bubbles and viscosity have been included in the model by UMC Utrecht. CFD calculations were performed. The incorporation of check valves in the model has also started.

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WP5 - Impact

- 13 Presentations in conferences
- 7 publications in international magazines, open access
- Two newsletters published on the webpage
- Two case studies published on the webpage
- Standardization participation:
  - TC84/SC6 - ISO 7886 2
  - IEC/TC 62 D - IEC60601-2-24
  - ISO TC 48/WG4 – New ISO 8655-9
  - TC48/WG5 - ISO 23783-2
  - ISO/TC 150/SC 6 - ISO14708-4
  - AAMI TIR101
  - ISO TC 210 - ISO TR 24971:2019

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https://zenodo.org/communities/medd2

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THANK YOU

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