METROLOGY for DRUG DELIVERY

MEDD II
Drugmetrology.com

Development & validation of calibration techniques for ultra-low flow rates below 100 nL/min

18HLT08 MeDD II – WP1

14th Workshop Low Liquid Flows in Medical Technology
Lübeck, Germany, September 15th, 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

Ultra-low flow rates – nano flows

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Flow rates from 100 nL/min and down to 5 nL/min => 6 µL/h to 0.3 µL/h

Flow rate **100 nL/min**,
time to get the droplet: **50 min**

Flow rate **5 nL/min**,
time to get the droplet: **16.7 hours**

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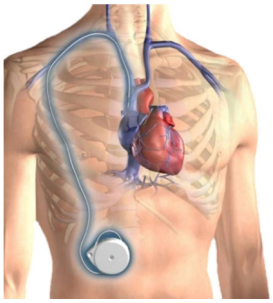
Ultra-low flow applications

Implantable Infusion Pumps



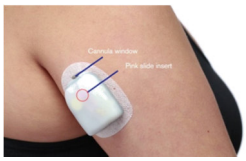
https://doorbuyer.net/823967/18-United-therapeutics-corporation.html

https://www.medtronic.com/us-en/healthcare-professionals/products/neurological/drug-infusion-systems/synchromed-ii.html

https://bmccancer.biomedcentral.com/articles/10.1186/s12885-019-5515-8/figures/2

Insulin Pumps

https://mygbi.org/articles/sales-of-medtronic-paradigm-pump-line-discontinued



https://www.omnipod.com/fr-ch/educational-resources/videos

https://www.medtronic-diabetes.co.uk/insulin-pump-therapy/minimed-640g-system

Flow rates range : 0.048 mL/day to 3 mL/day
$Q_{L\ min}$= 33 nL/min

Basal rate: 0.02 U/h → 50 U/h
$Q_{L\ min}$= 3 nL/min

CETIAT
ensemble, innover et valider

Development of metrology infrastructure for ultra-low flow rates

- Develop new techniques for measurement of **flow rates down to 5 nL/min** for steady and fast changing dynamic 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.

Ultra-low flow rate techniques

Gravimetric method

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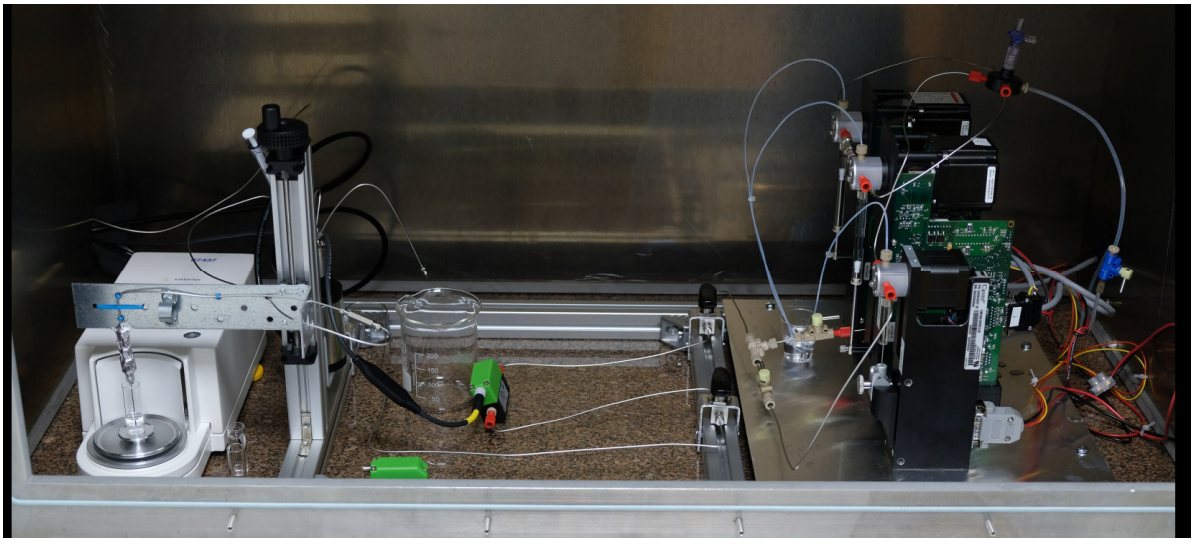
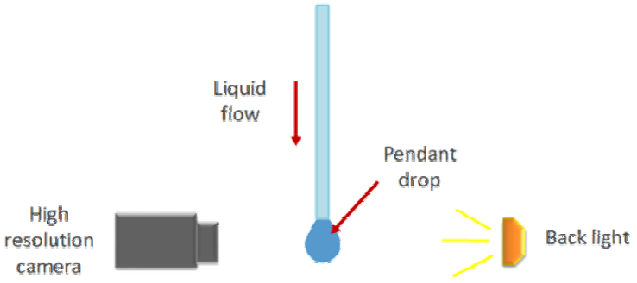
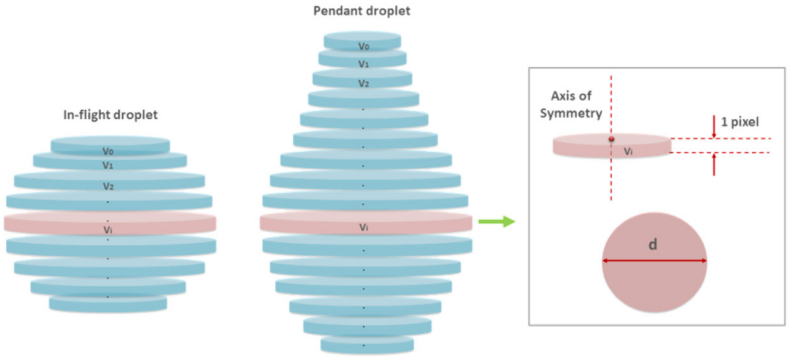
Steady flow rates down to ≈ 15 nL/min with uncertainties of the order of 1 % (*k*=2)
Dynamic flow rates down to ≈ 20 nL/min with uncertainties from 2 to 5 % (*k*=2)



Optical nano-flow standards: pendant drop





Measurement of the increase in the droplet's volume over time under a liquid flow

$$Q_V = \frac{\Delta V_{droplet}}{\Delta t}$$

Volume is calculated by the sum of cylindrical portions with a height of 1 pixel, assuming that the droplet is symmetrical about its axis.

The relative expanded (k=2) uncertainty is between 10 % and 3 % for 0.1 µL/min to 1 µL/min

Interface tracking standard

Measuring the displacement of a liquid/air or liquid/liquid interface as a function of time moving inside a glass capillary tube connected to a flow generating device

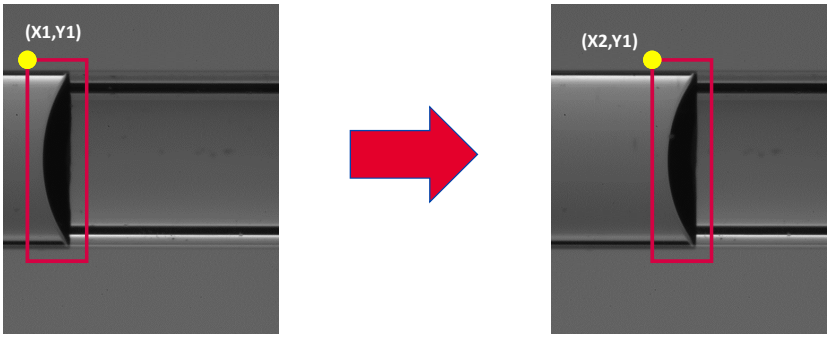
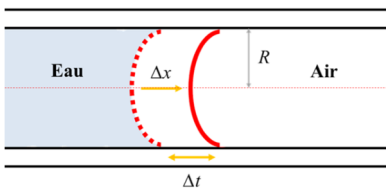


Image1 (t1)

Image2 (t2)

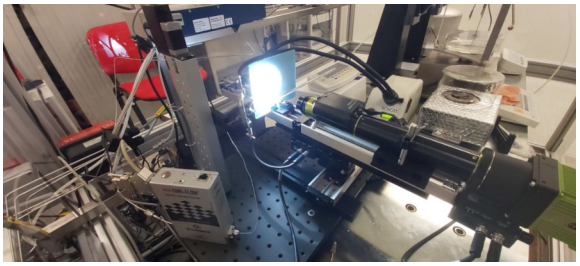
$$\Delta X(t1, t2) = X2 - X1$$

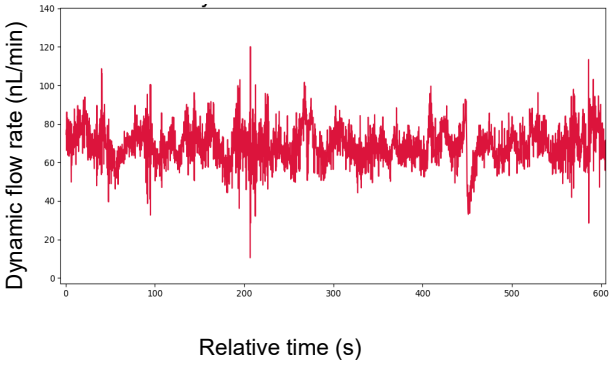


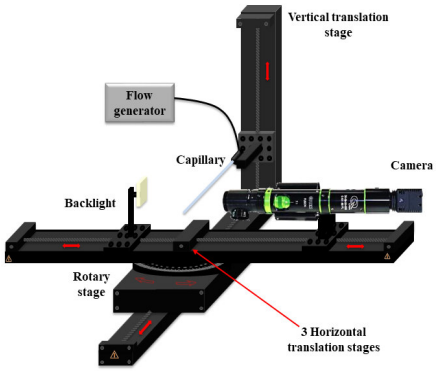
$$Q_{volumetric} = \pi \frac{d^2}{4} . v = \pi \frac{d^2}{4} . \frac{\Delta x}{\Delta t}$$

The relative expanded (*k*=2) uncertainty is between 10 % and 1 % for flow rates of 1 nL/min to 16 µL/min.

Interface tracking standard







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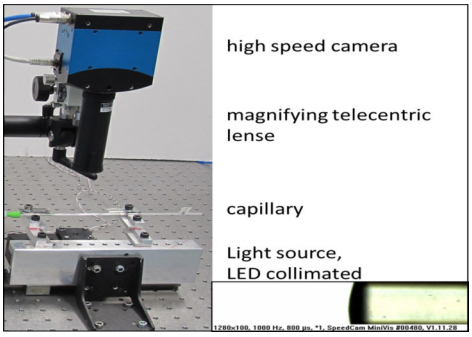

TECHNISCHE HOCHSCHULE LÜBECK

Displacement methods – piston prover

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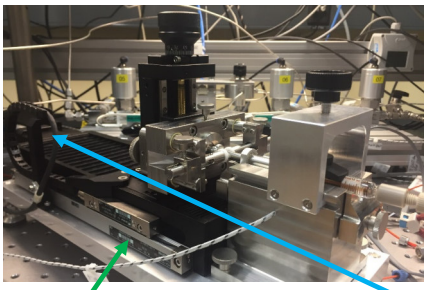
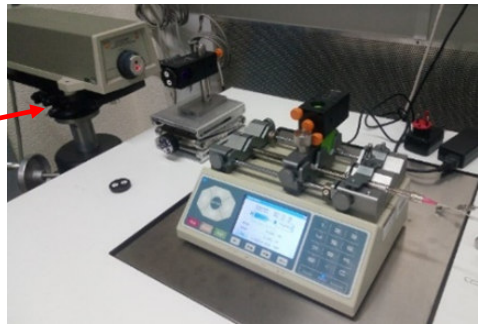


RI. SE

Linear Measuring system

Motor Encoder Signal

Interferometer directly



This method can go down to 1.6 nL/min with 2 % (k=2) uncertainty.

IPQ

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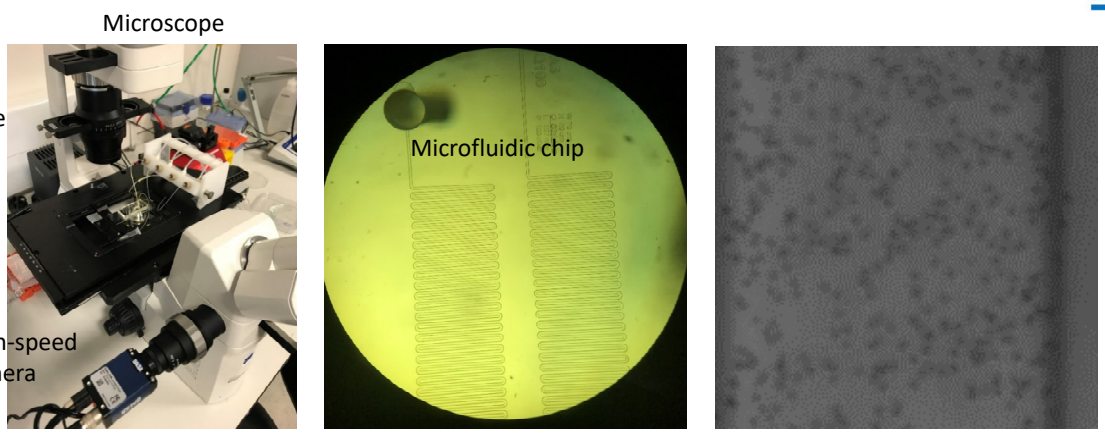
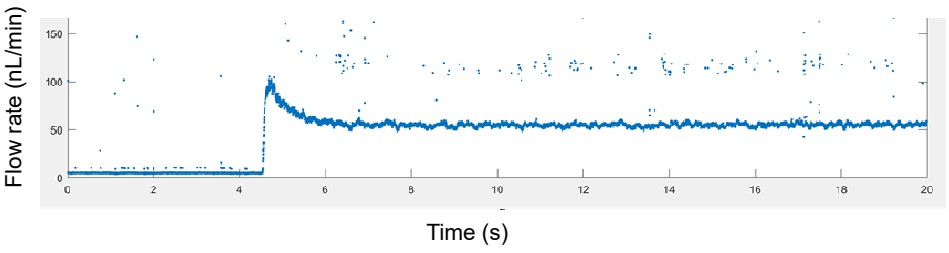
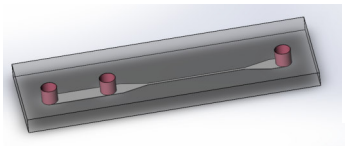
Micro-Particle Imaging Velocimetry (µ-PIV)

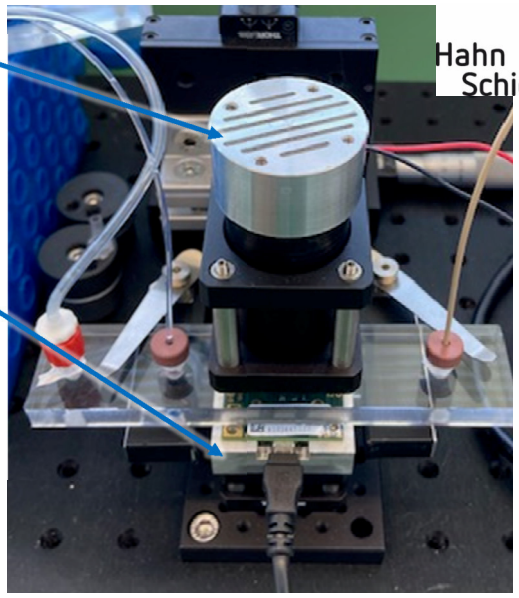


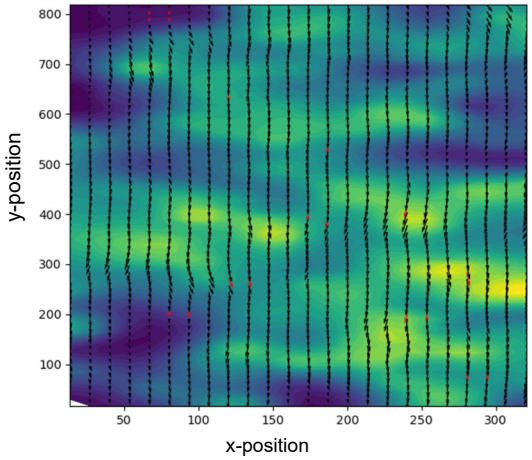


Compact holographic µ-PIV



- neMESYS pump (Cetoni GmbH)
- LED light source - wavelength 455 nm, power 549 mW
- Sample carrier - custom made channel 25 x 0.6 x 0.1 mm
- Imaging Sensor - optical area 6.413 x 4.589 mm, pixel size: 1.67 µm, frame rate: 3.2 fps





Instantaneous velocity profile at 50 nL/min

Colour scheme ranges from 56.3 nL/min (brightest) to 45.8 nL/min (darkest)

Further info on ultra-low flow rate techniques:

- Comprehensive report on the new calibration methods for steady and dynamic flow rates:
  - "*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
  - www.drugmetrology.com/the-first-deliverable-of-project-medd-ii-is-now-available/
- Online Workshop on Microflow Calibration Methods (Nov 2020)
  - Presentations available at:

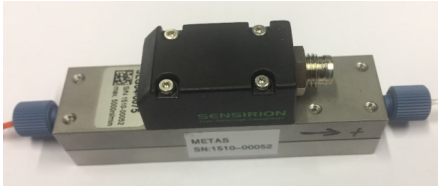
https://drugmetrology.com/on-line-workshop-on-microflow-calibration-methods/

Validation of ultra-low flow rate techniques

Intercomparison exercise using 3 transfer standards

Sensirion thermal flow meter SLG64-0075

- 1.5 µL/min to 20 nL/min



Cetoni Nemesys Pump

- 100 µL & 10 µL glass syringes
- 100 to 5 nL/min

Bronkhorst thermal flow meter L01-20D

- 1.5 µL/min to 20 nL/min

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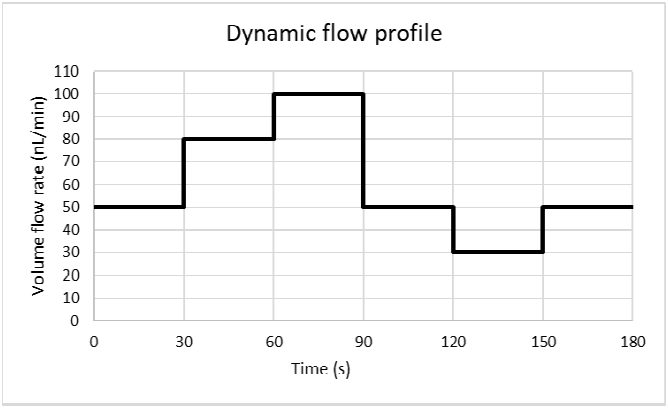
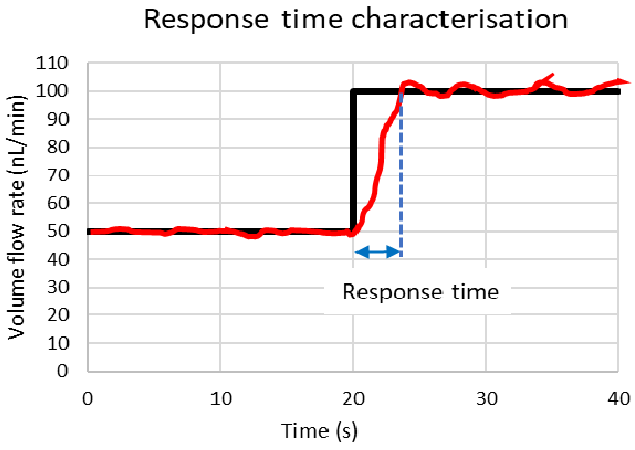
Static & dynamic flow testing





Flow meter / generator	Static testing	Dynamic testing	Response time characterization
SLG64-0075			
L01-20D			
Cetoni syringe pump			

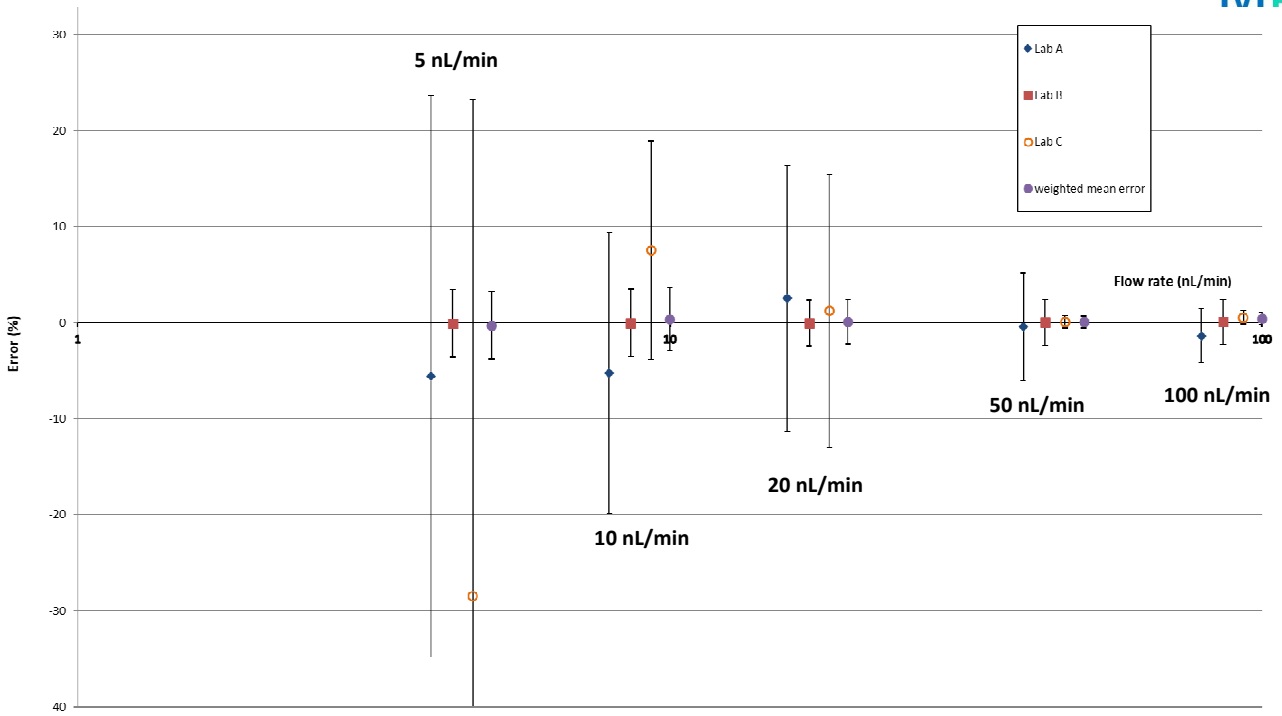
Validation of new techniques

- Intercomparison exercise using 3 transfer standards

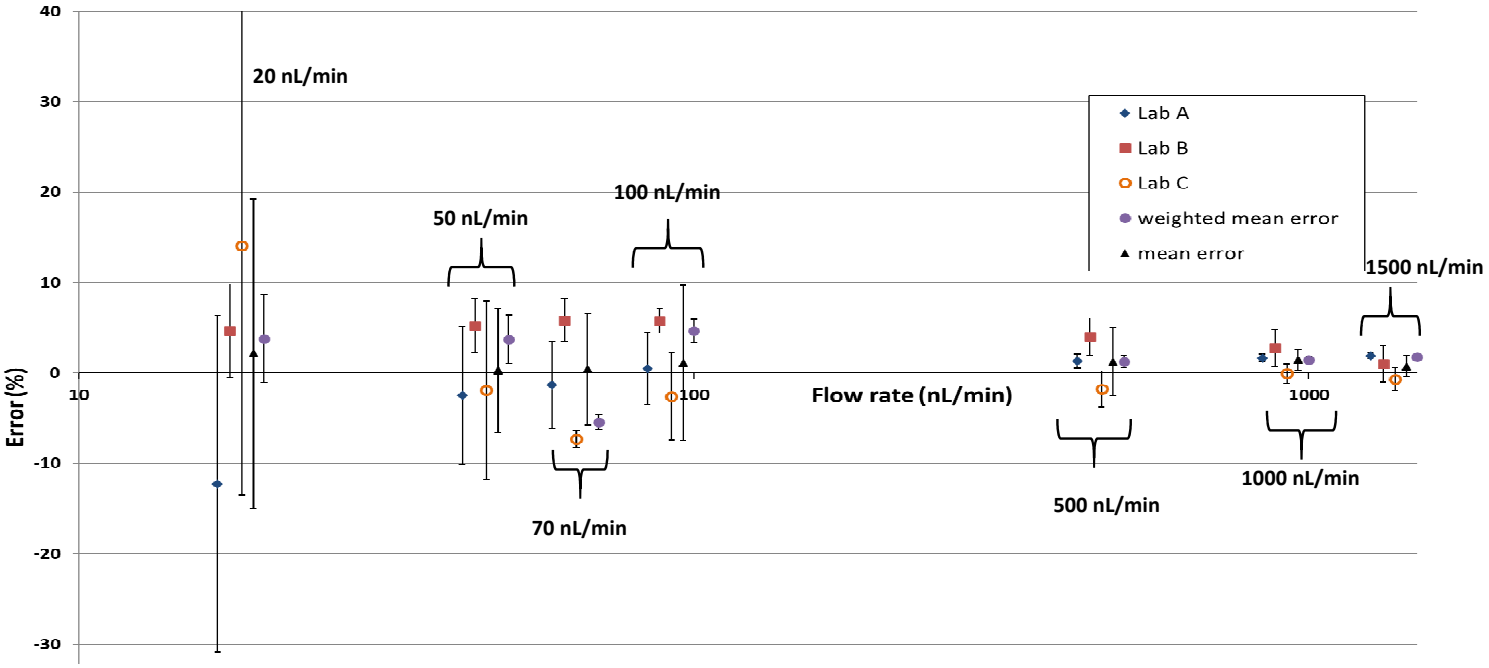
Bronkhorst High-Tech, L01-20D, 2 weeks
Sensirion AG, thermal SLG64-0075, 2 weeks
Cetoni, NemeSys syringe pump, 2 weeks
Shipping period (not drawn in schedule), 1 week

Week	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
METAS																												
IPQ																												
CETIAT																												
STRATH																												
THL																												
HSG-MIT																												
RISE																												
DTI																												
BHT																												

Comparison – Cetoni syringe pump 5 to 100 nL/min



Comparison – Sensirion thermal flow meter 20 to 1500 nL/min



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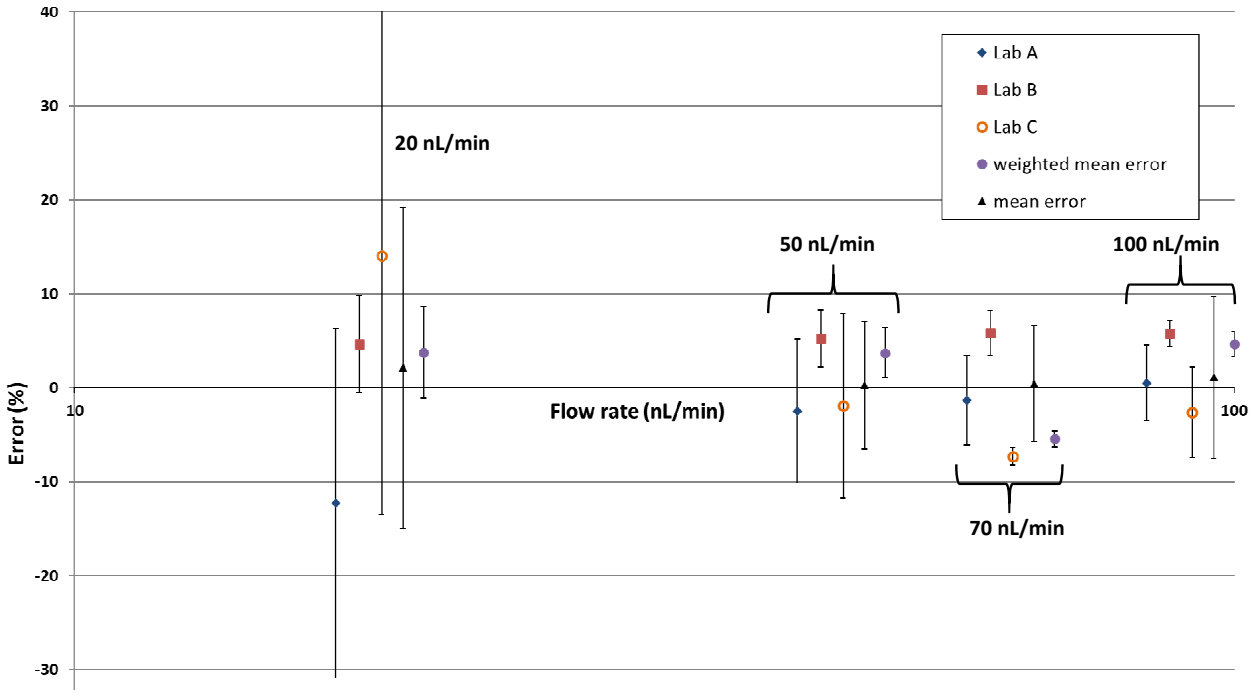
Comparison – Sensirion thermal flow meter 20 to 100 nL/min



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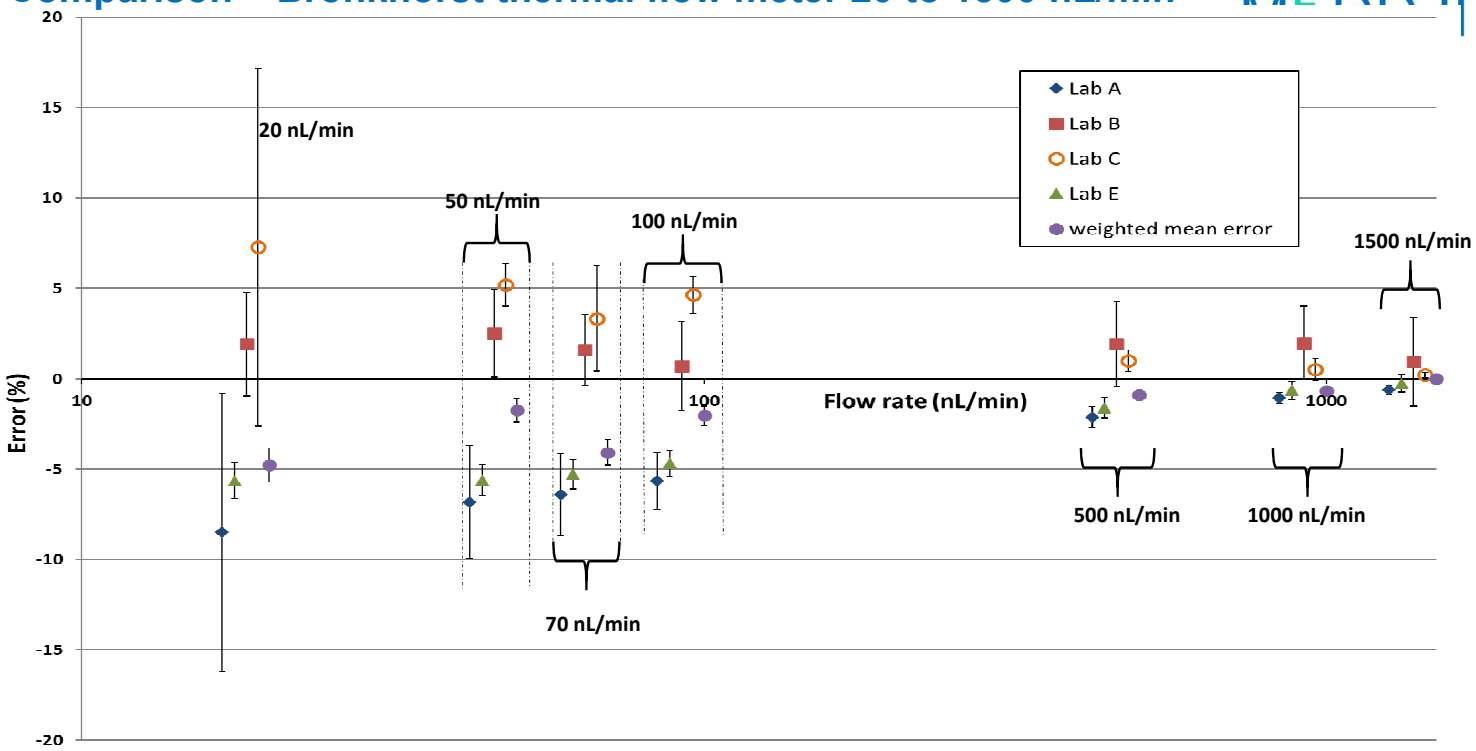
Comparison – Bronkhorst thermal flow meter 20 to 1500 nL/min



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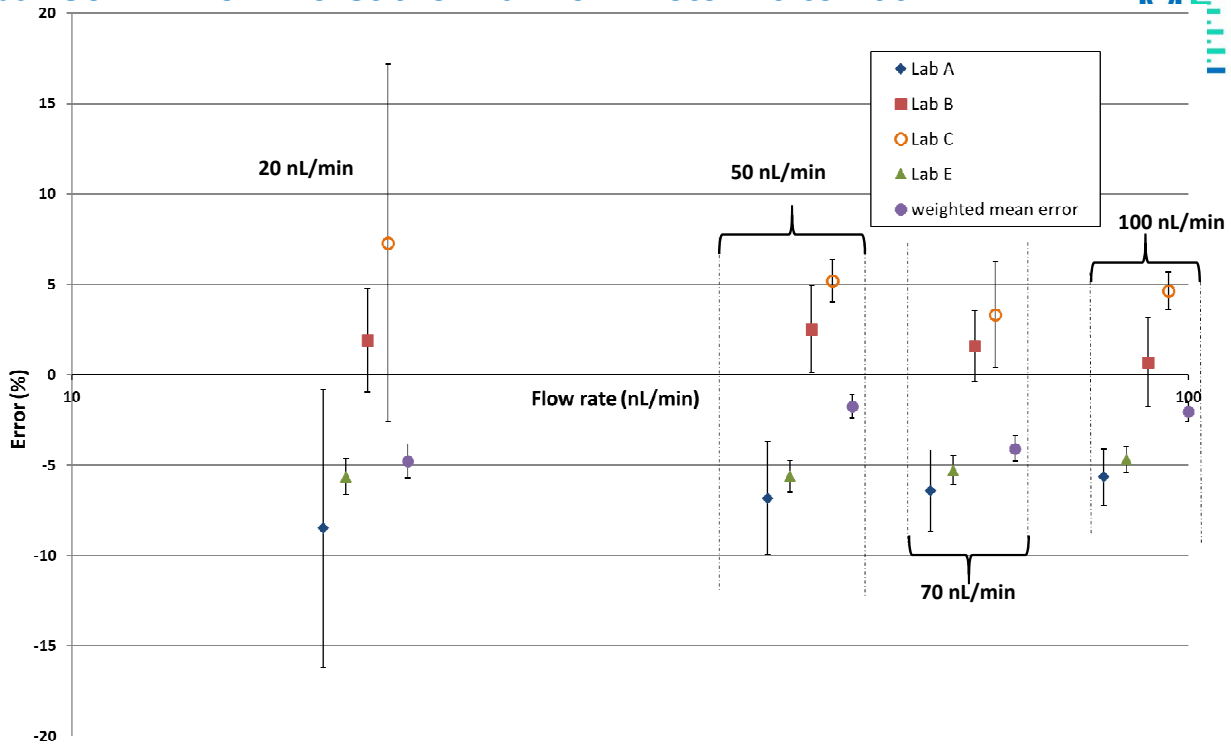
Comparison – Bronkhorst thermal flow meter 20 to 100 nL/min



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Summary

- 8 organisations developed techniques to measure flow rates below 100 nL/min
  - Gravimetric
  - Optical pendant drop
  - Interface tracking
  - Displacement
  - Micro-PIV
- Techniques validated in intercomparison exercise using 3 transfer standards
  - 2 thermal flow meters
  - 1 syringe pump
- Results currently being collected and analysed
- 1st draft of results in Nov 2021

THANK YOU