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MEASURING OF MICRO-FLOWS AND CALIBRATING CORRESPONDING MEASUREMENT-DEVICES IN MEDICAL TECHNOLOGY

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22/2 2023

Domestic water meter

Insulin pump

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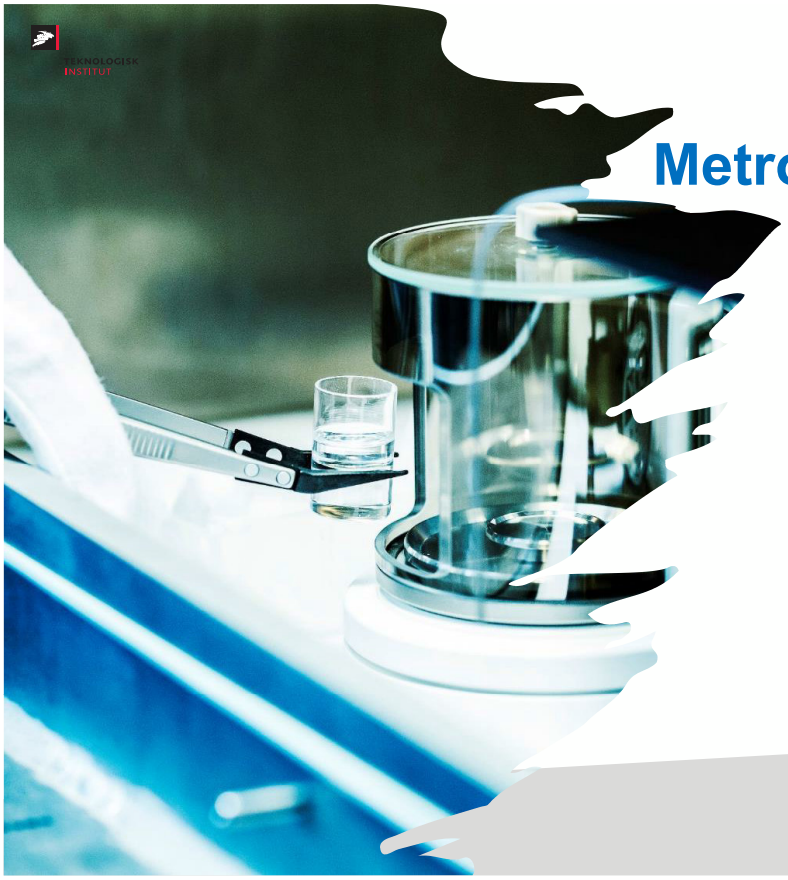

Metrology for Drug Delivery II - OVERVIEW

The overall objective of this project is to enable traceable measurements of the volume, flow rate and pressure of existing drug delivery devices (and other medical devices, like infusion pump analysers and organ on a chip) and in-line sensors that work at a flow rate lower than 100 nL/min. This project will also investigate fast changing flow rates, liquid mixing behaviour and occlusion phenomena in multi-infusion systems in order to improve the dosing accuracy in each infusion line.

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

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NEEDS AND MOTIVATION

PATIENT SAFETY

- **Infusion therapy** → Main form of therapy in health care.
- **Deviations** in medication dose into the patient bloodstream can have a **dramatic effect** leading to severe health damage or death
- Wide range of applications uses microfluidic solutions (infusion of vasoactive drugs, multi-infusion therapy, pre-term babies therapy, organ-on-a-chip technology, etc.).

The increasing implementations of novel microfluidic solutions in healthcare will require the development of a metrological infrastructure for validating quality and reproducibility.

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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Urmageren fra Zanzibar

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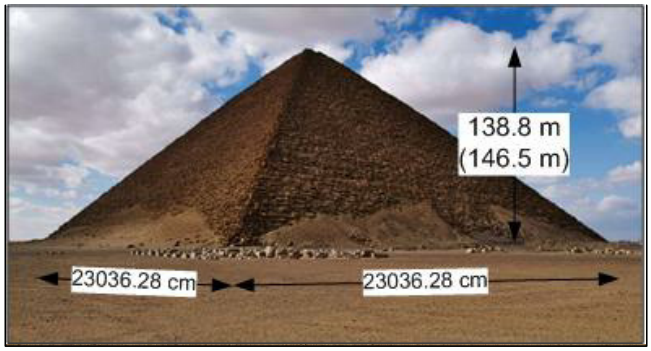
What is traceability in a metrological context?

- The Great Pyramid of Giza Built in the 26th century BC during a period of around 27 years
- Oldest and only existing of the "Seven Wonders of the Ancient World"



- The construction is an achievement in itself
- But without well-founded metrology, quality manuals and standards: how could it be done?

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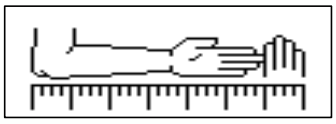
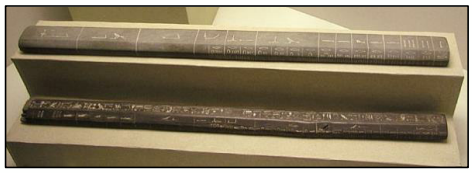
Step 1: Define a unit of length:



The cubit is based on the distance from the elbow to the middle finger of the ruling pharaoh (1 royal cubit = 523.5 to 529.2 mm)

- The royal cubit is divided into 7 palms
- A palm is divided into 4 fingers (called digit) that is: 28 digits for a cubit

Step 2: Realize the unit from its definition



Step 3: Make copies – and calibrate them by comparison

Result:
Deviation from horizontal < 15 mm
Base length: 230363 mm ± 57 mm

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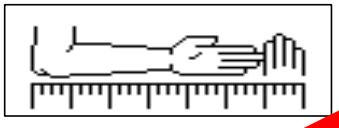

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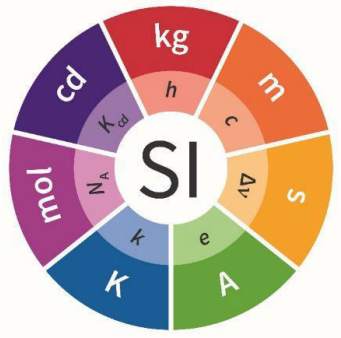
Traceability, calibration and quality control

SI-system (2019) Definition from physical constants



- the caesium hyperfine frequency $\Delta\nu$ 9 192 631 770 Hz
- the speed of light in vacuum c 299 792 458 m/s
- the Planck constant h $6.626\ 070\ 15 \times 10^{-34}$ J s
- the elementary charge e $1.602\ 176\ 634 \times 10^{-19}$ C
- the Boltzmann constant k $1.380\ 649 \times 10^{-23}$ J/K
- the Avogadro constant N_A $6.022\ 140\ 76 \times 10^{23}$ mol^{-1}
- the luminous efficacy of a defined visible radiation K_{cd} 683 lm/W

It is by fixing the exact numerical value of each that the unit becomes defined, since the product of the **numerical value** and the **unit** must equal the **value** of the constant.

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Metrological Traceability

- Metrological traceability is a property of a measurement result whereby the result can be related to a reference through a documented unbroken chain of calibrations, each contributing to the measurement uncertainty
- Measurement uncertainty ensures that a measurement result is related to a reference on a "higher level" that in the end is compared with a primary realization of the unit – measurement uncertainty is a measure of the quality of a measurement.
- Thus, traceability is needed in order to make trustworthy measurements on all levels independent of method or instrument type.

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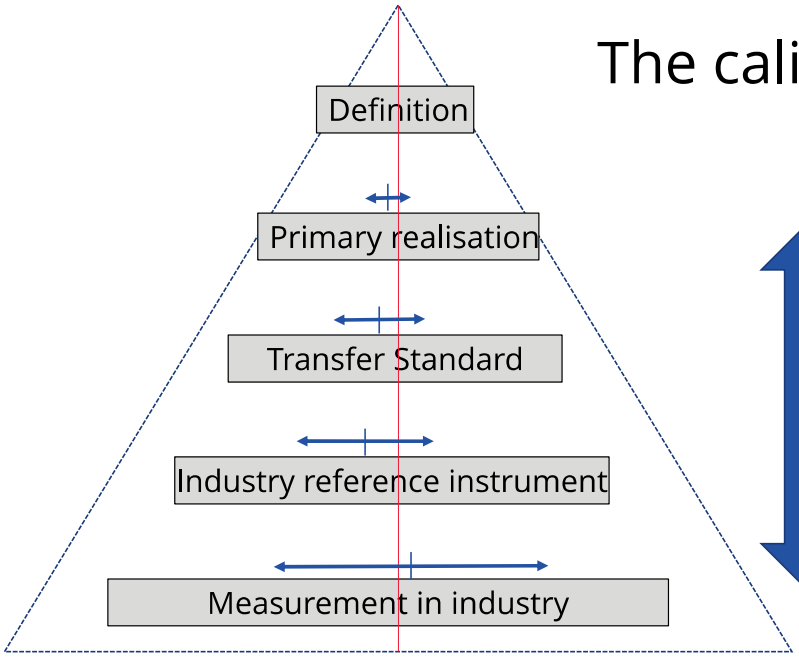
The calibration hierarchy



For every step in the chain of calibrations the uncertainty increases

Too low uncertainties "breaks" the traceability chain

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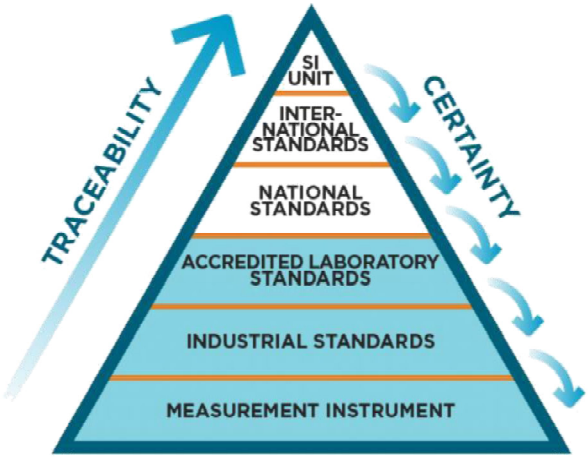
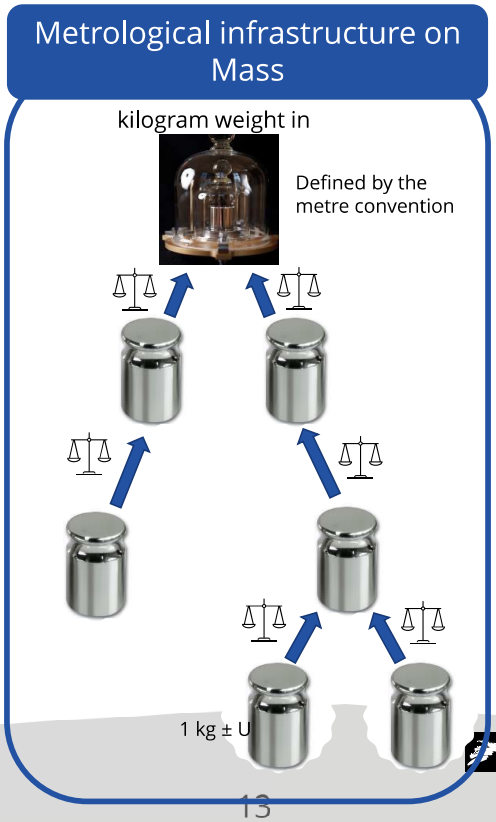
METROLOGY EXAMPLE

- Metrology is the scientific study of measurement. It establishes a tracebility chain to a commonly agreed reference for all basic units





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Uncertainty of calibration

- By calibrating a measurement instrument the error with respect to a reference is found
- This measurement has an uncertainty

Reference value °C	Reference value %rh	Indication %rh	Error %rh	Uncertainty %rh
0.08	61.62	56.50	-5.12	0.73
24.97	24.70	23.70	-1.00	0.21
25.01	60.79	55.70	-5.09	0.40
25.02	90.85	83.40	-7.45	0.57
50.17	60.70	56.65	-4.05	0.74

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Ideal micro-flow traceability chain

Definition
($m^3/s \rightarrow \mu L/hr$)

Primary method
(Gravimetric, ...)

Transfer standard
(Pump, IDA, Flowmeter,...)

Clinical devices
Insulin pumps, Diffusion device, ...

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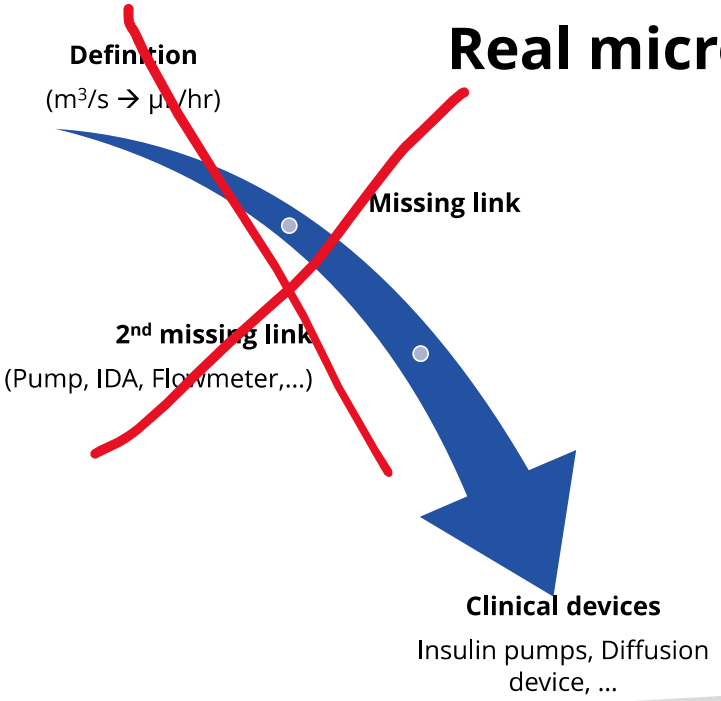
Real micro-flow ~~traceability chain~~



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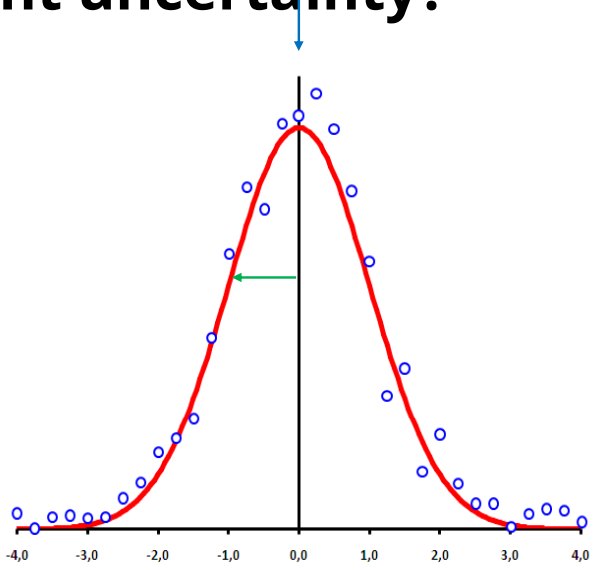
What is measurement uncertainty?

- parameter characterizing the dispersion of the quantity values being attributed to a measurand (the mean value)



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Microflow sizes

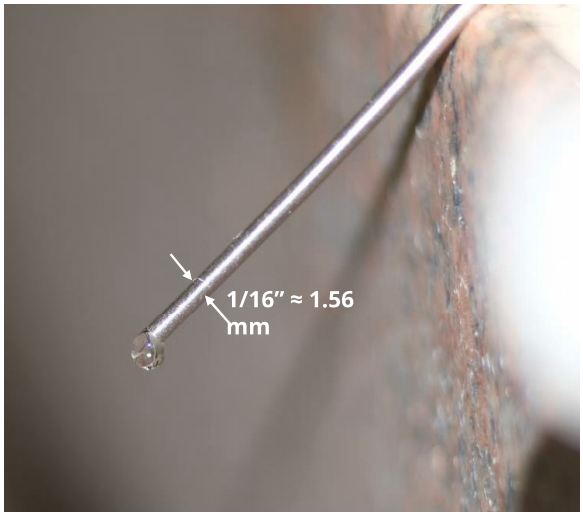
- Gravimetric method

- **Flow rates from 17 µL/min and down to 15 nL/min**

Flow rate **17 µL/min**, time to get the droplet: **18 sec**

Flow rate **15 nL/min**, time to get the droplet: **5.6 hours**

Size **5 µL**



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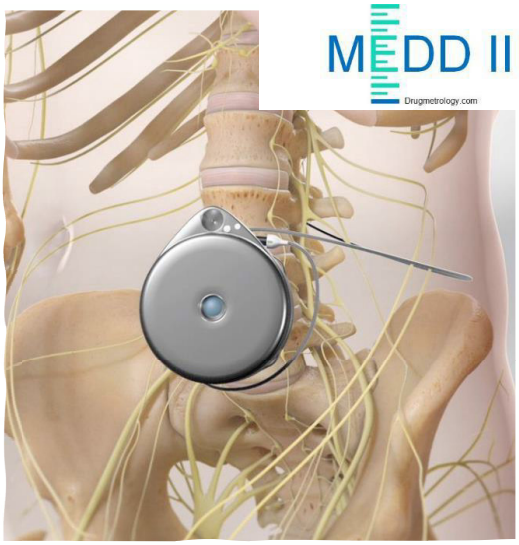
MEDICAL DEVICES

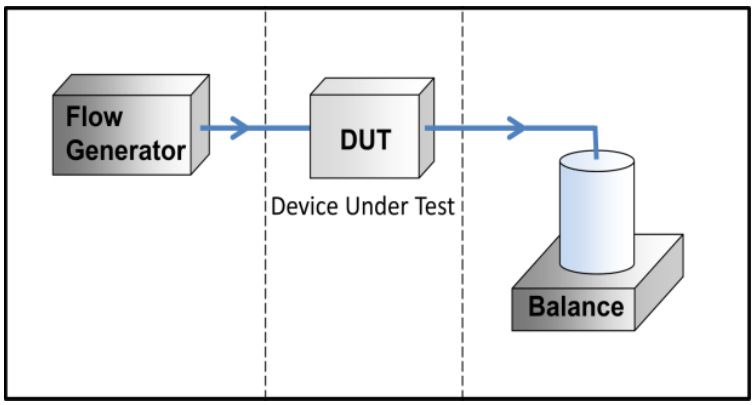
FLOW RATE IS A CRUCIAL PARAMETER

- Implantable pain pump (≈ 20 µL/hr)
- Insulin pump (≈ 10 µL/hr)
- Syringe pump (> 0.1 mL/hr)
- Infusion device analyser (IDA)



Calibration: Gravimetric method

- The gravimetric method relies on weighing the mass of the working fluid delivered by the instrument under test for a set time.
  - Steady flow (down to 1.2 µL/hr ≈ 17 nL/min)



Gravimetric calibration method

Steady flow:

$$Q_{vol} = \frac{V_{delivered}}{\Delta time}$$

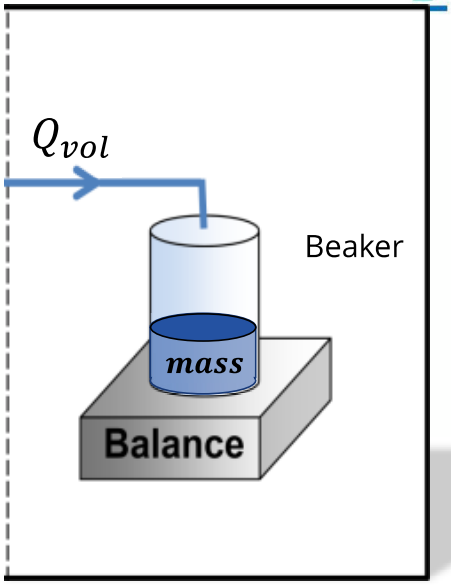
$$V_{delivered} = V_{finish} - V_{start}$$

$$\Delta time = t_{finish} - t_{start}$$

$$V = \frac{mass}{density}$$

Most medical devices specifies flow rates as volume flow

Density is a function of temperature and is different from liquid to liquid

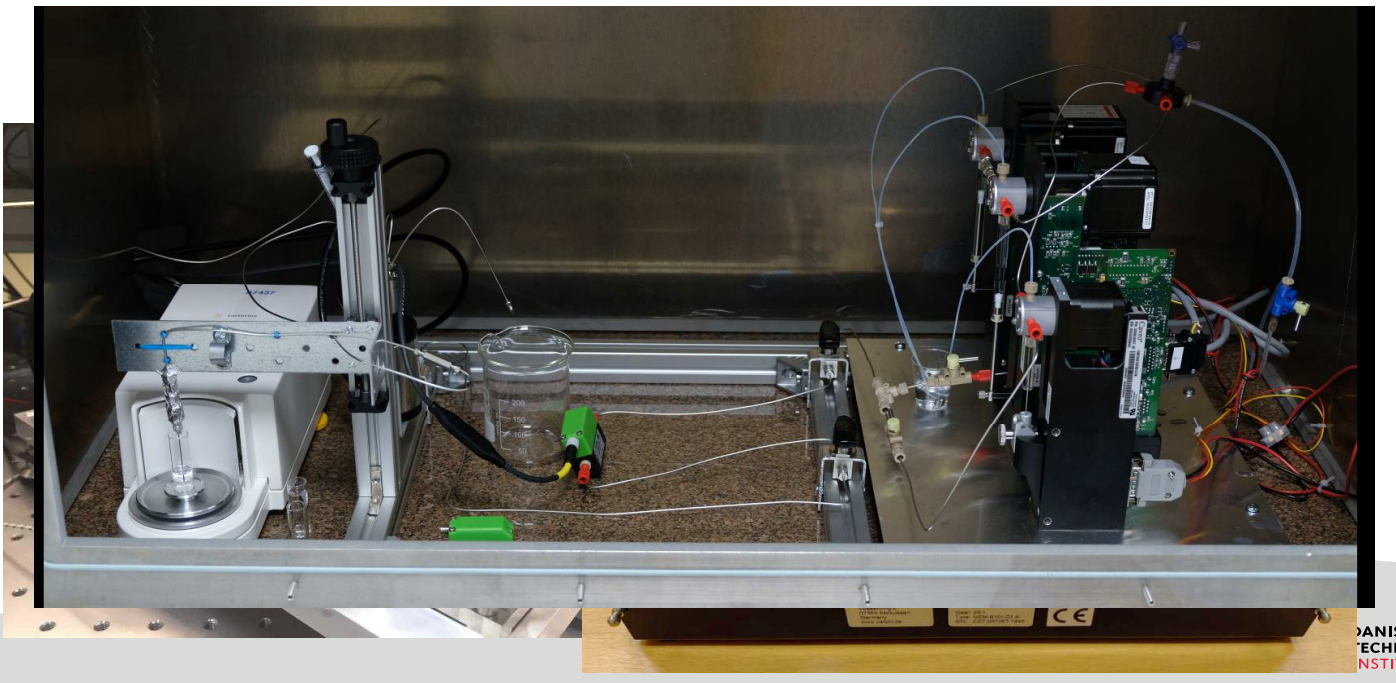


Parameters influencing the measurements

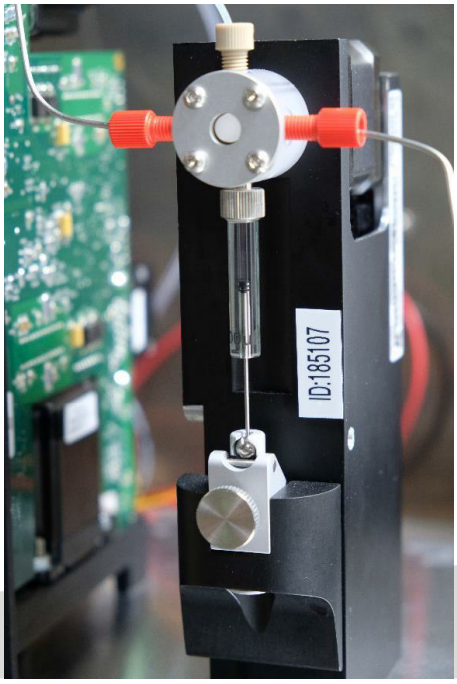
- Evaporation
- Degassing water
- Priming the tubing and the flow meter under test
- Flow rate stability
- Timing
- Temperature stability
- Buoyancy correction of the delivered liquid
- Buoyancy correction due to the immersed tube into the liquid

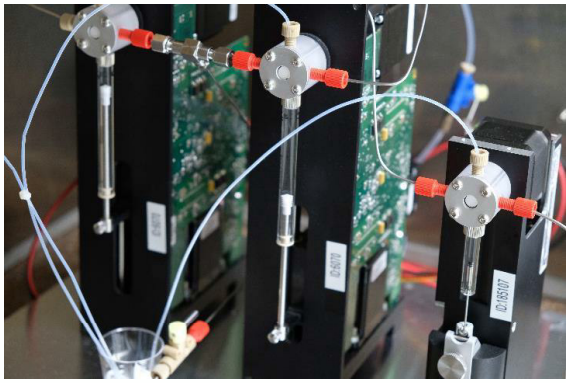
- Jet force out of the immersion tube
- Linearity of the balance
- Drift of the balance

Calibration setups
- Precision syringe and gravimetric



PUMP FOR CALIBRATION OF FLOW METER





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FLOW METER (REF. OR DUT)

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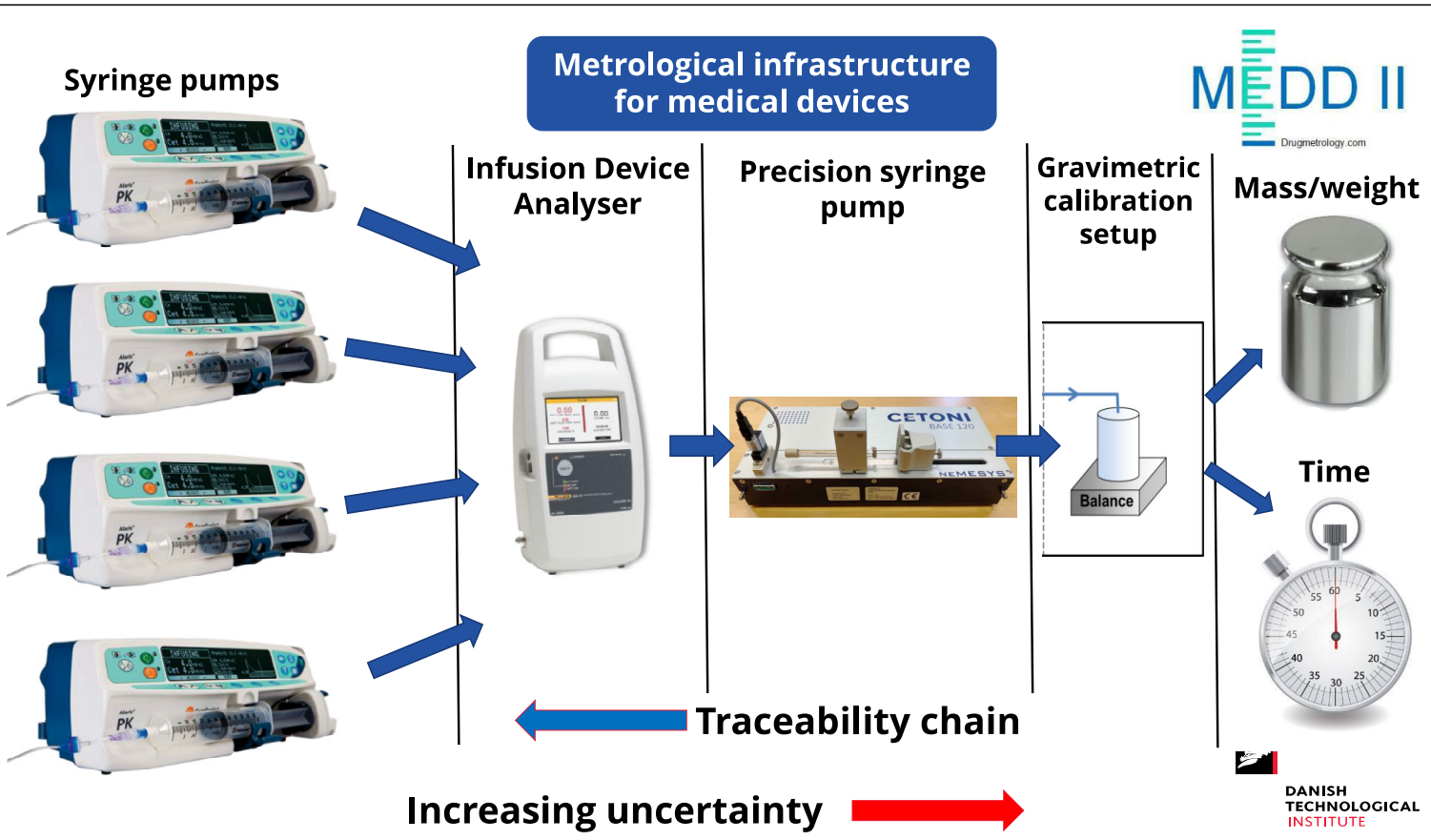
GRAVIMETRIC REFERENCE ANALYSIS



Case: Test example of small medical device

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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

Calculation of flow: linear regression vs. weight change, $W_{end} - W_{start}$

Remarks: Using regression may cause errors

1. Regression is not representative if the flow is not approximately constant
2. Calculation of average flow will not be correct
3. Dose estimate ($= Flow \times \Delta t$) is not correct

→ see graphs for insulin pump at 10 µl/hr

- Start/end should not be in the step region of the graph: Otherwise, this may lead to increased scatter (lack of repeatability)
- The result of the analysis depends strongly on the sample period being equal to the pump shot cycle (trumpet-curve analysis)

Pump properties: Short- and long-term variations in flow

Short-term variations

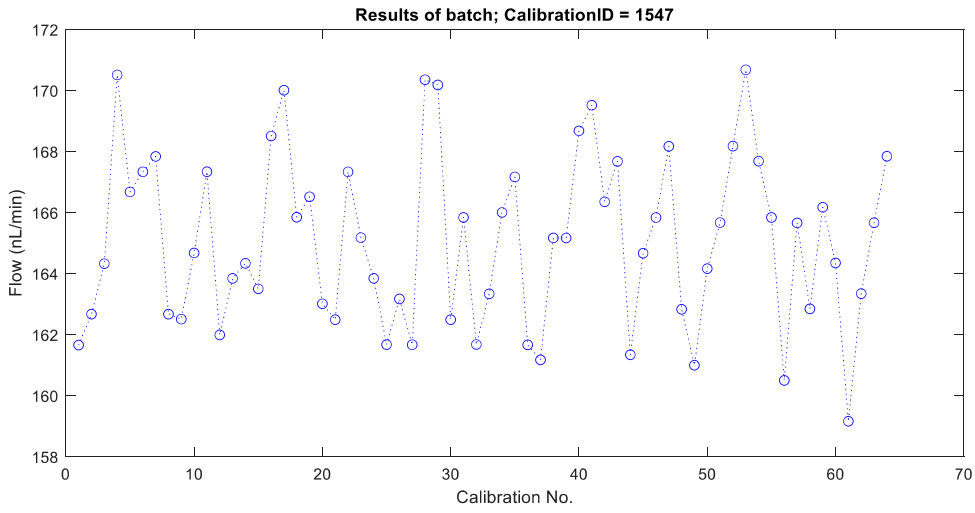
1. Main cause: Pump shot cycle
2. This example
   - 3 min for flow of 10 µl/hr
   - 15 min for flow of 1 µl/hr
3. Measured: At least 10 subsequent shot are used for the determination of the shot cycle

Long-term variations, possible causes:

1. Spindle
   1. In this example: 1 turn of the spindle ≈ 60 µl
   2. Illustration: See next slide
2. Variation in the syringe diameter
3. Elasticity (syringe, piston, driving mechanism, tubing)

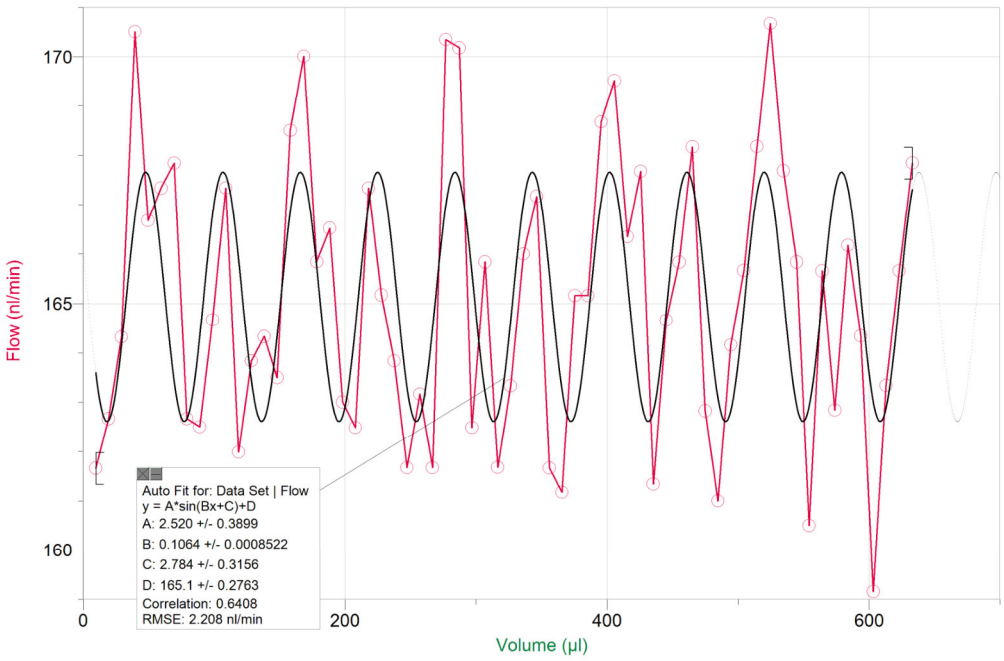
Long-term variation

- 10 µl/hr, 60 min/measurement



Long-term variation

- Period of main cycle is about 60 µl, cf. curve fit



$$C = \frac{2\pi}{T}$$

$$T = \frac{2\pi}{C} = \frac{2\pi}{0.106} = 59\ \mu l$$

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Analysis:

1. Pharmacokinetic analysis (PKA)

2. Trumpet-curve analysis (TCA)

References

1. PKA: AAMI TIR101: 2021
2. TCA: IEC 60601-2-24 (2012)

PKA

- Evaluates the dose volume as in steady state (input = output)
  - Input: Pumped liquid
  - Output: Exponential decay, characterized by a decay time, t_D
  - Result = relative standard deviation of dose volume, CV%
- Addition parameters
  - Min and Max error (%) in sliding window of 1 hr
  - Error (%)

TCA

- Evaluates the flow rate of the pumped liquid
- Trumpet curve
  - Min and Max error (%) in different sliding window
  - Window size: integer number of pump shot cycles
- Addition parameters
  - Error (%)

→ In this analysis: CV% is calculated too

→ All errors are calculated with respect to set value of flow rate and given in %

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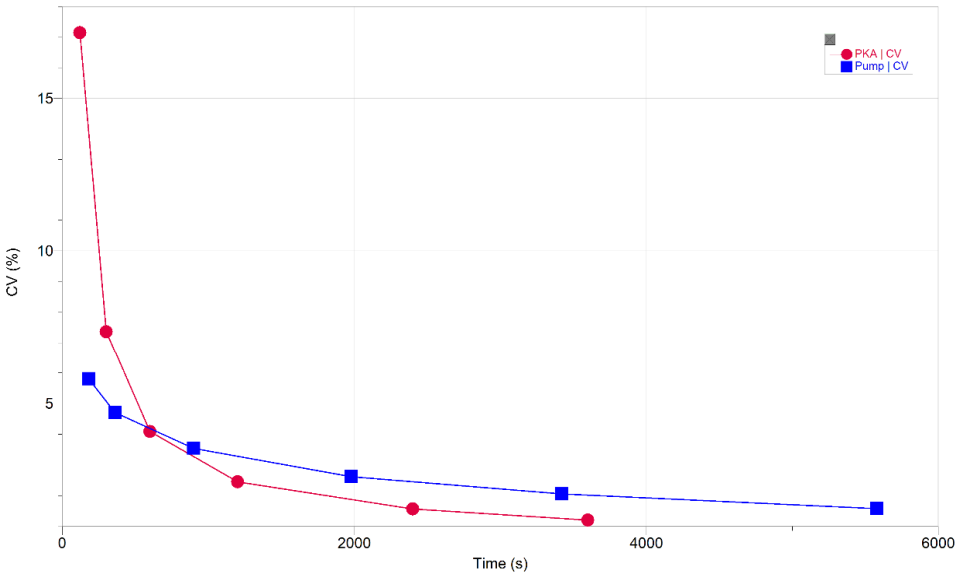
PKA vs TCA

Example: Analysis of insulin pump.

- Flow: 10 µl/hr
- Data recorded 2 – 13 hr after start
- Definition of "Time" (horizontal axis)
  - PKA: Decay time
  - TCA: Length of sliding window



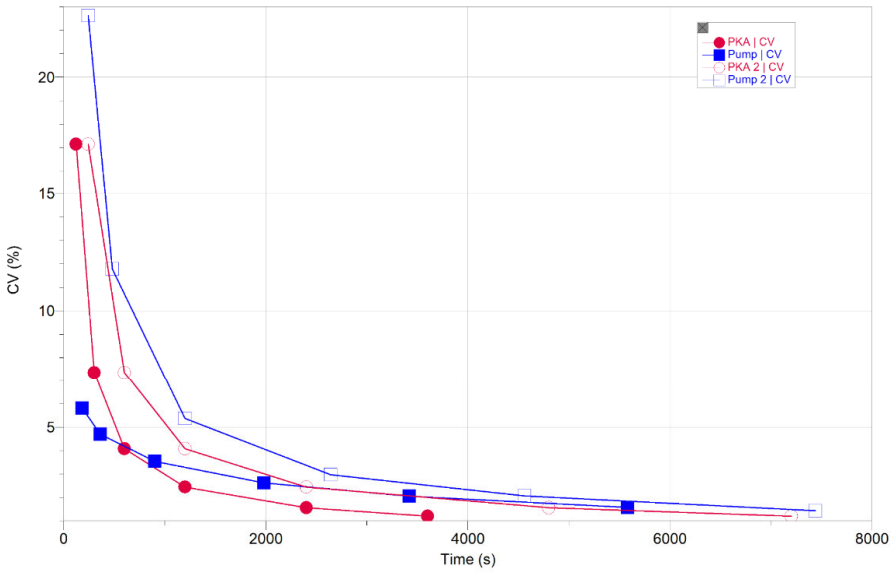
PKA vs TCA

Why is the TCA lowest for small time values?

→ Matching of sample period and pump shot cycle
→ If match is not present the TCA will yield much larger error values

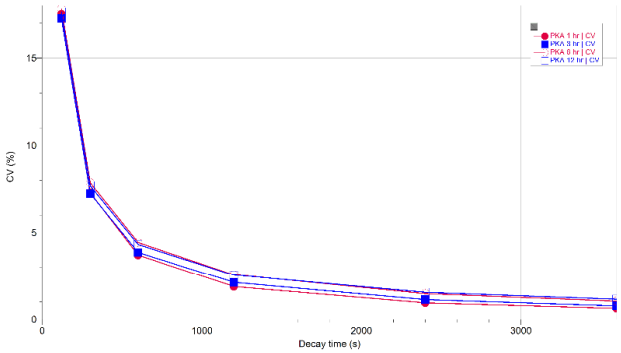
Description of graph:
As above + trumpet-curve analysis with analysis window (4 min) different from the pump shot cycle (3 min) (blue empty squares).

10 µl/hr



Length of test period

- Ex: 10 µl/h



- Top figure: PKA conducted for different test periods: 1, 3, 6, 12 hr
- Pump rotation period ≈ 6 hr
- Bottom figure: The CV% value for the largest decay time in the PKA as a function of the test period
- Observation: The value of CV% reaches a plateau at ≈ 6 hr, corresponding to a full pump period

→ Conclusion: The test period should ideally cover at least on full rotation period

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WHY DON'T WE, THEN, SEE MORE ACCIDENTAL INCIDENCES?

- Awareness on the limitations of the devices e.g., accuracy
- The patient is surveilled on more parameters e.g., during surgery
  - Pulse, blood pressure, visually, blood gases, etc.
- Well-educated and trained personnel
- Treatment response is very different from patient to patient

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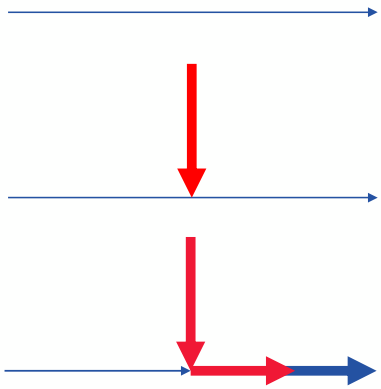
NO CALIBRATION: SO WHAT ????

Direct result: Wrong dose

- Unintended effect (e.g. through very large/small dose)
- Incorrect assessment of effect of drug (e.g. drug ineffective vs. dose too small)
- Not possible to transfer of result of investigation from one hospital to another



- Also: Flow mixing

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ACKNOWLEDGMENT

FMET
Establishing Metrology Standards in Microfluidic Devices

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