# Primary standard for nano flow rates

*Metrology for drug delivery*

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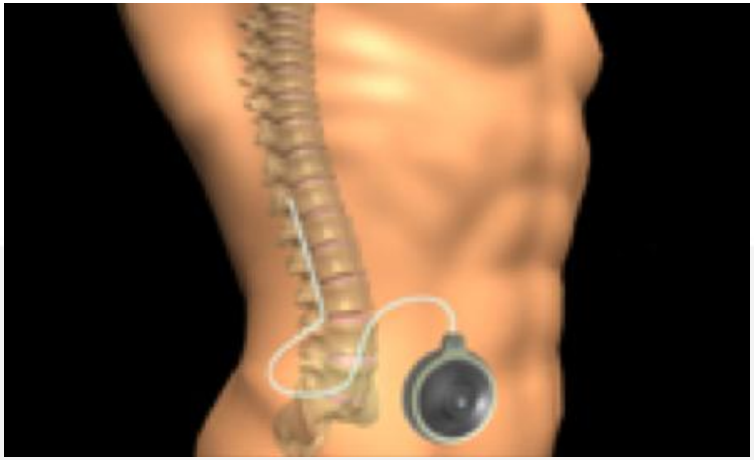
# Motivation

*Underestimated risks Infusion technology*

- In various studies infusion technology is considered a technology with underestimated risks
- Adverse incidents
  - (Head)ache
  - …
  - Death
- Challenges
  - Setting and controlling ultra-low flow rates (< 1 ml/h)
  - Setting and controlling the outflow concentration for multi-pump infusion
  - Drug delivery device characteristics

# Motivation

*Low to ultra-low flow rates*



Applications

- Drug delivery for patients with fluid restrictions
- Critical drug delivery, e.g. anesthetics, vasoactive drugs, insulin, hormone therapy
- Drug delivery by means of implanted infusion pumps

Challenge: difficult to measure, set and control flow rate

# Motivation

## *Other*

Multipump infusion

- Effective concentration drugs (larger flow rates influence smaller ones)
- Long start up time to reach steady flow

General characteristics

- Calibration methods not always suitable (stopwatch plus balance)
- Effective flow rate of the complete drug delivery device (pump plus accessories)
- Significant dependency on fluid and process parameters

# Goals

- To develop metrological tools that can help to improve drug delivery
  - Validated primary standards for liquid flow rates from 1 nl/min to 100 ml/min
  - Reliable transfer standard for drug delivery device calibration on site
  - Calibration services for flow rates from 1 nl/min up to 100 ml/min
- Metrological assessment commercial flow meters
- Metrological assessment drug delivery devices

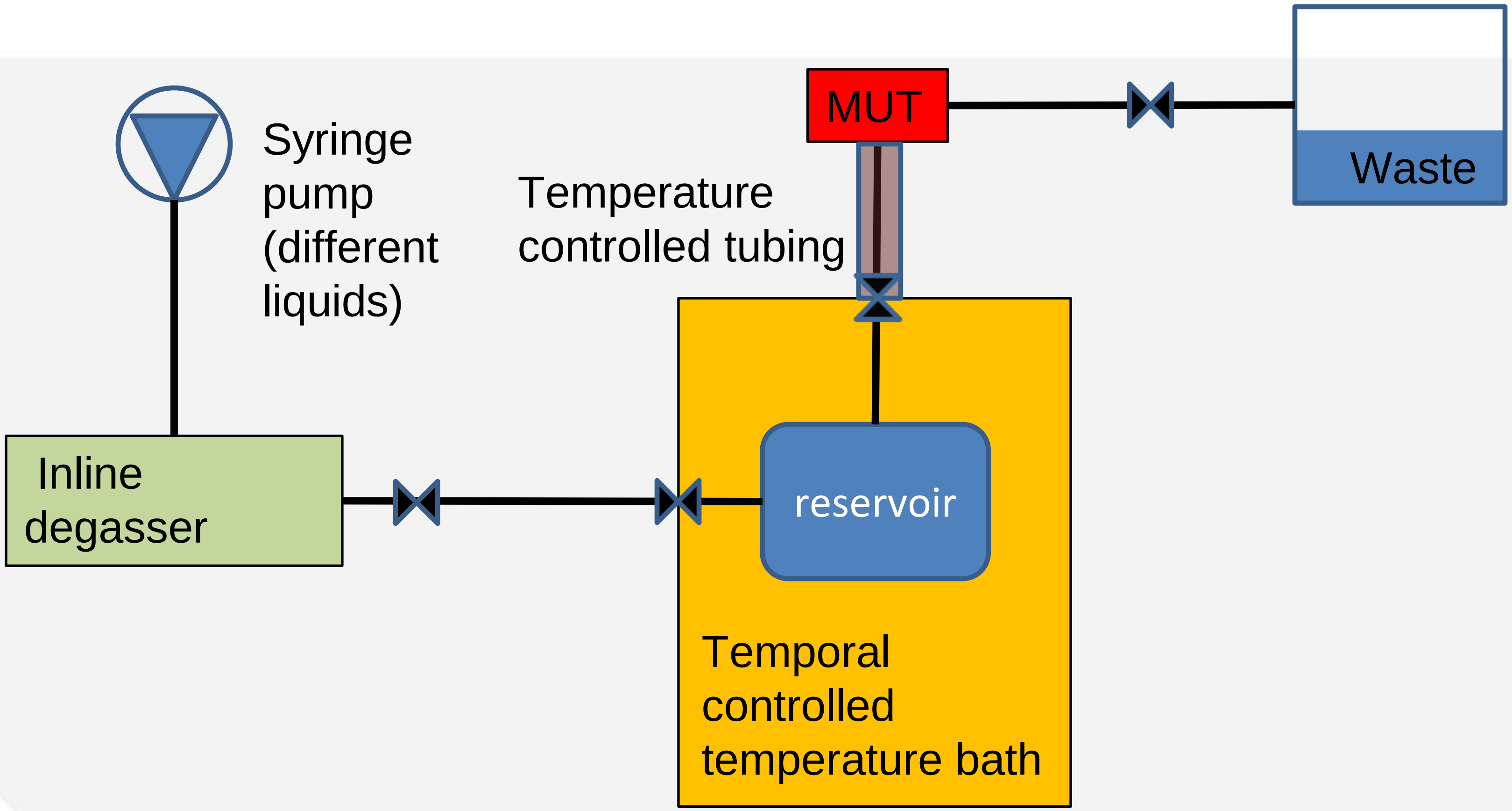
# Development primary standard 1 to 1000 nl/min

*Overview remainder presentation*

- Sketch and working principles
- Design
- Theory/ traceability

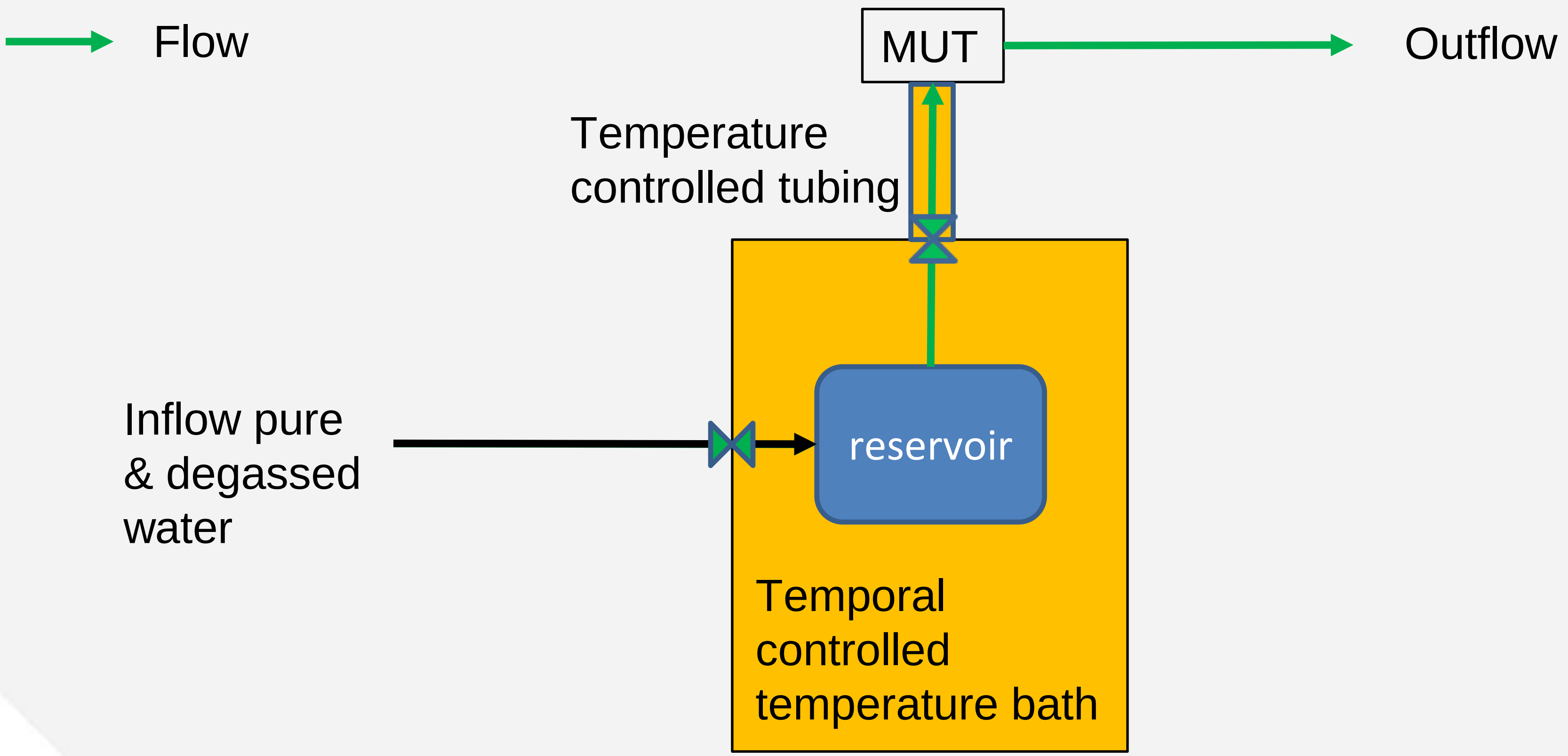


# Sketch set up



# Operation

## *Calibration*



# Development primary standard 1 to 1000 nl/min

*Overview remainder presentation*

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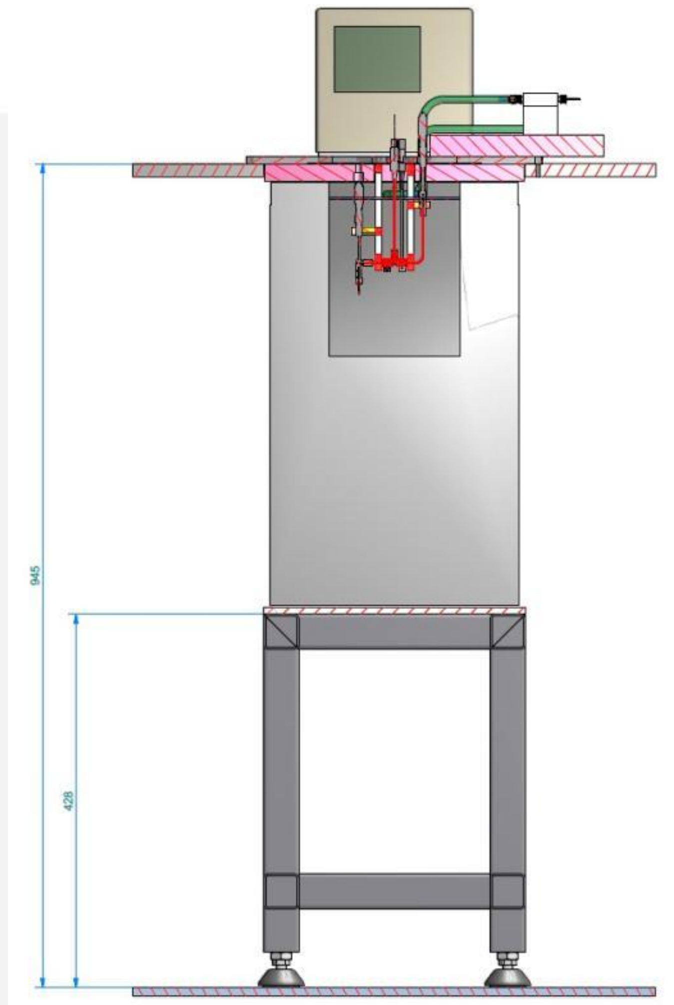
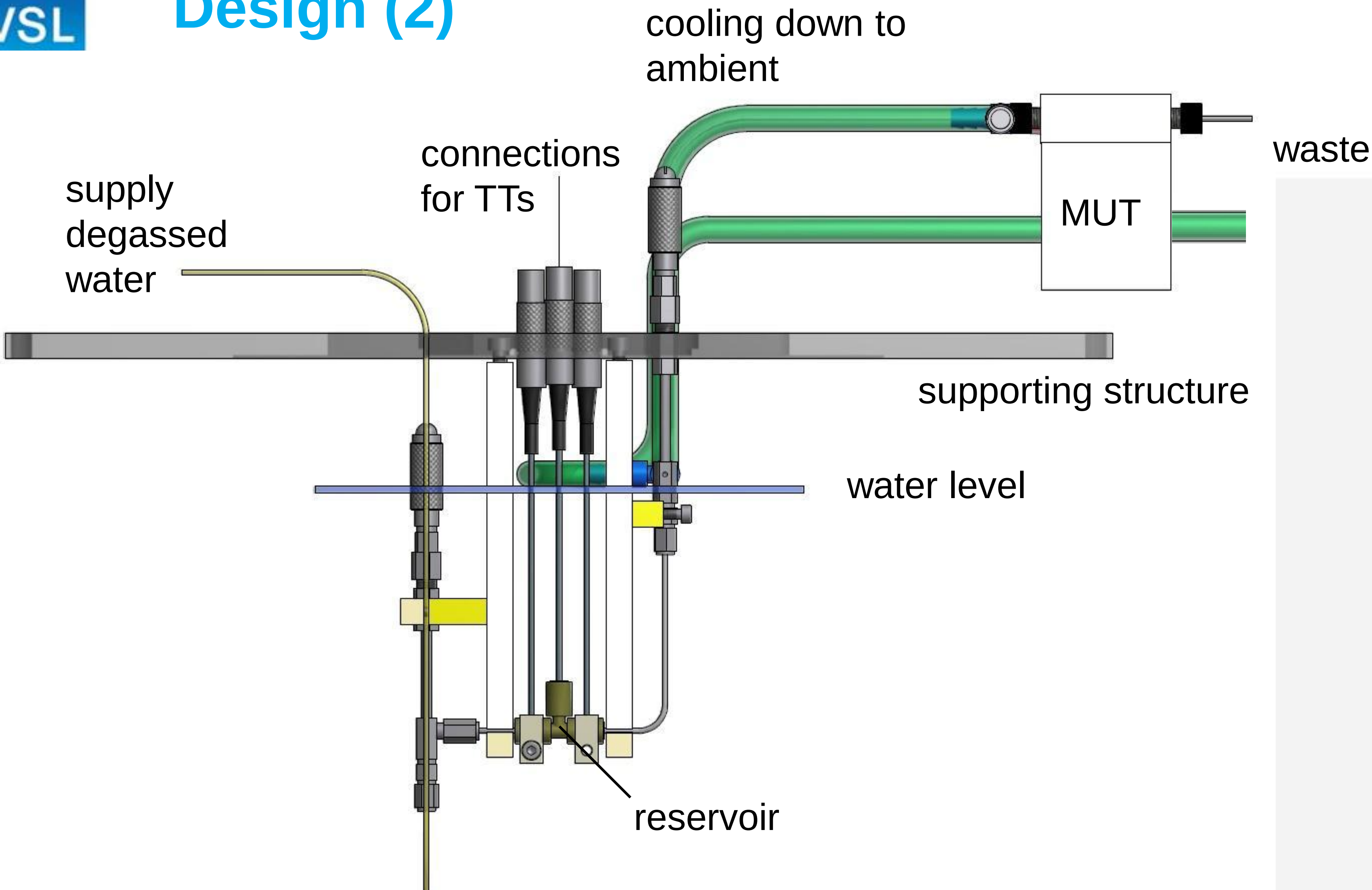
# Design (1)



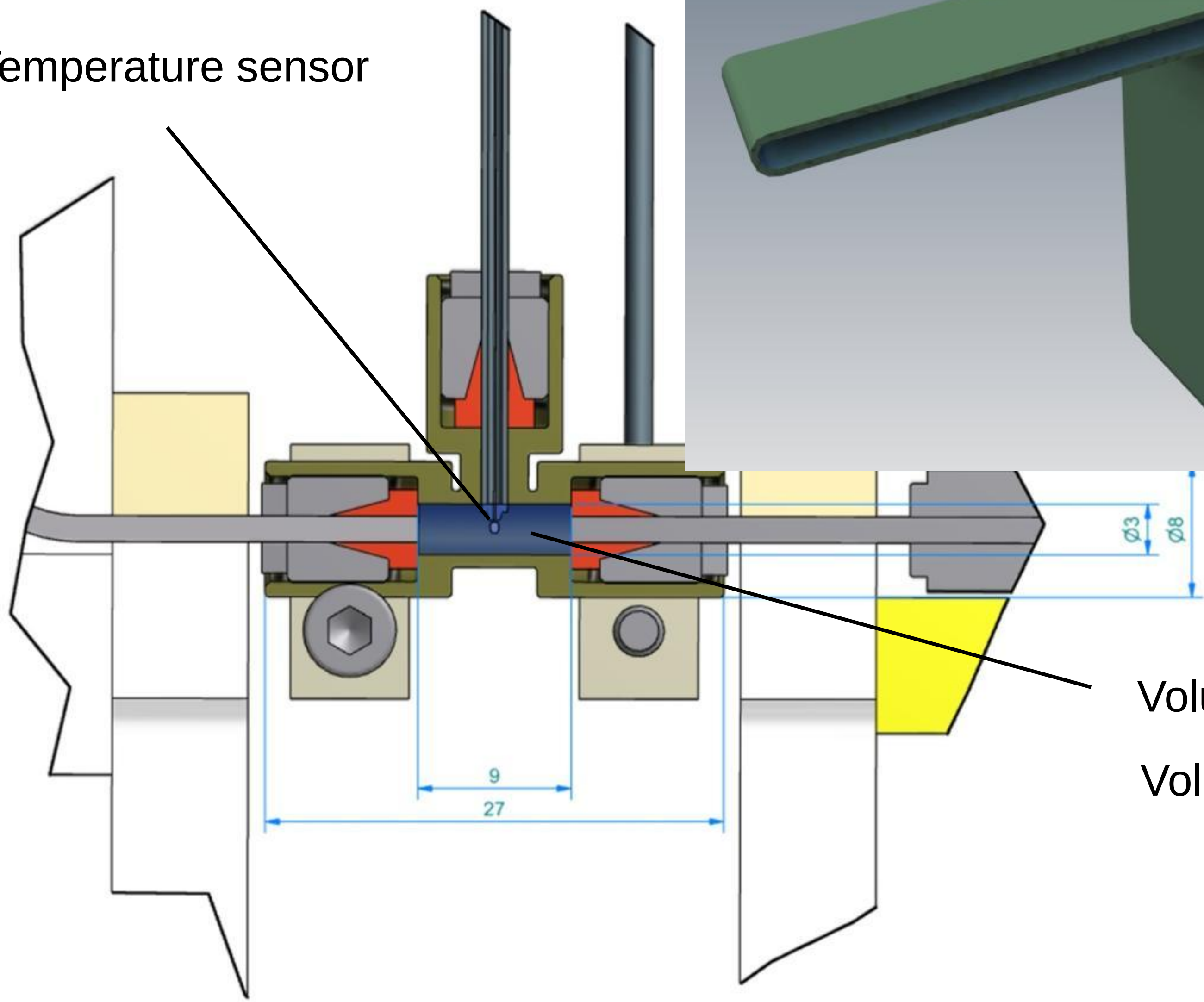
# Design (2)

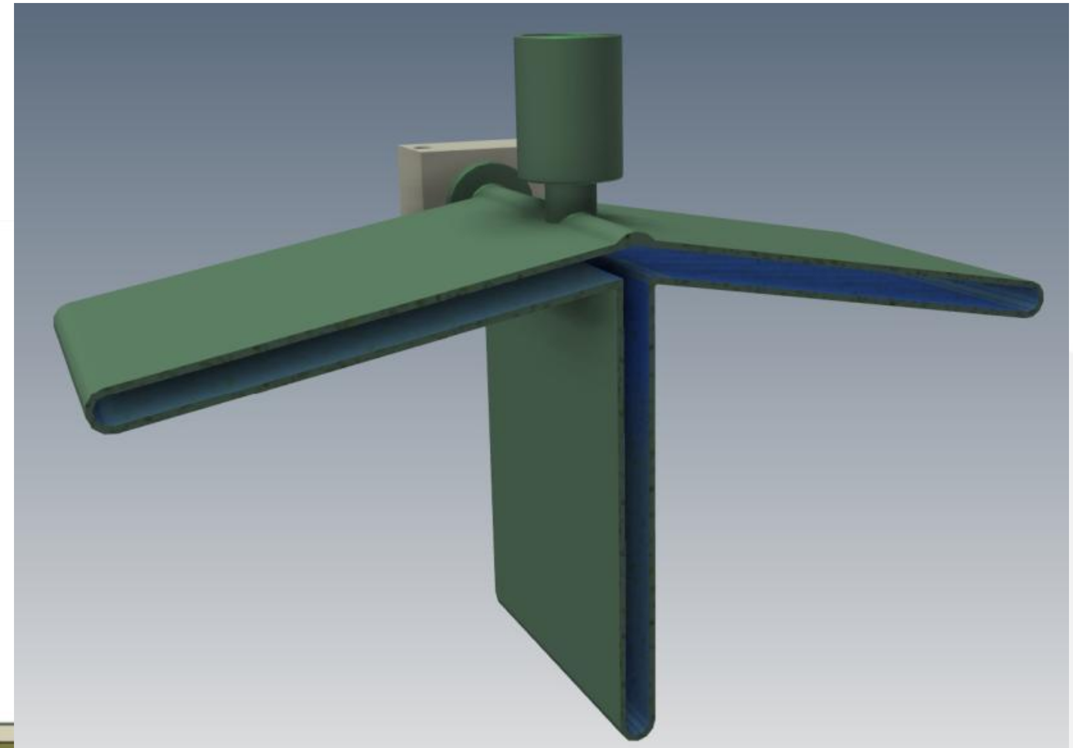


cooling down to ambient
connections for TTs
supply degassed water
waste
MUT
supporting structure
water level
reservoir

# Design (3)

Temperature sensor



Volume is 7500 mm$^3$

Volume is 60 mm$^3$

Volume is 1000 mm$^3$

# Development primary standard 1 to 1000 nl/min

*Overview remainder presentation*

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- Theory/ traceability

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# Theoretical model

## *Basics*

Volume given by: $V = \dfrac{m}{\rho}$

Volume flow due to volume expansion: $Q = \dfrac{\partial V}{\partial t} = -\dfrac{m}{\rho^2}\dfrac{\partial \rho}{\partial t}$

Working out the equations: $Q = -\dfrac{mk}{\rho^2}\left(\dfrac{\partial \rho}{\partial T}\right)_p$

Traceability through empty and full measurement

$m$ mass, function of time

$k$ temperature gradient, function of time

$\rho$ density, function of temperature

Traceability through the Tanaka equation for density (for pure water as function of temperature)

$\left(\dfrac{\partial \rho}{\partial T}\right)_p$ partial derivative density w.r.t. temperature at constant pressure

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# Theoretical model

## *Corrections*

Flow rate at the **exit** of the reservoir:

$$Q = -\frac{mk}{\rho^2} B$$

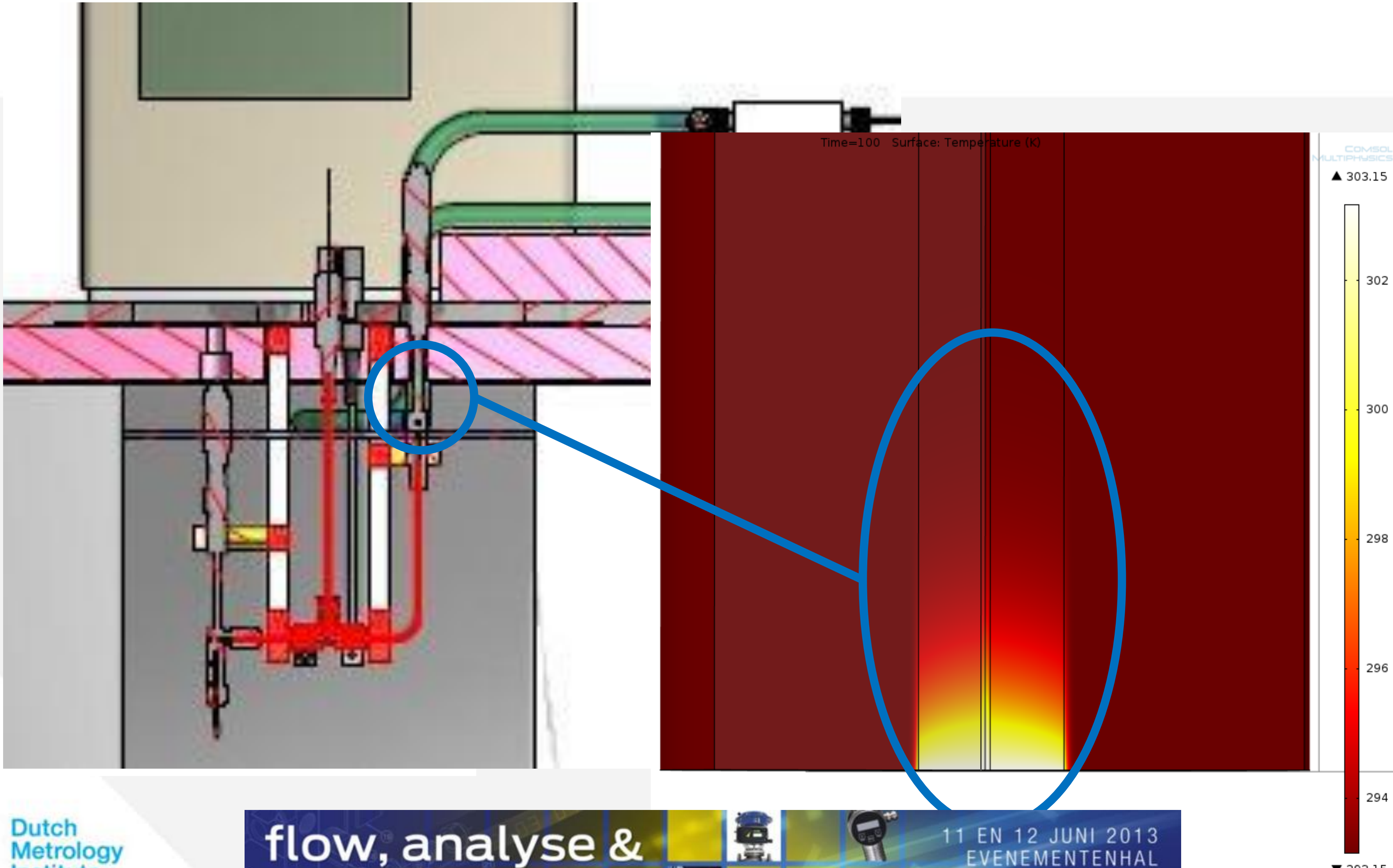
Required corrections

- Reservoir expansion (Titanium cell)
- Cooling down fluid elements (after leaving the bath)
- Spatial variation in temperature (spatial variation thermal expansion coefficient)
- Spatial variation in temperature gradient (spatial variation expansion rate)
- COMSOL (carried out by partner NMI)



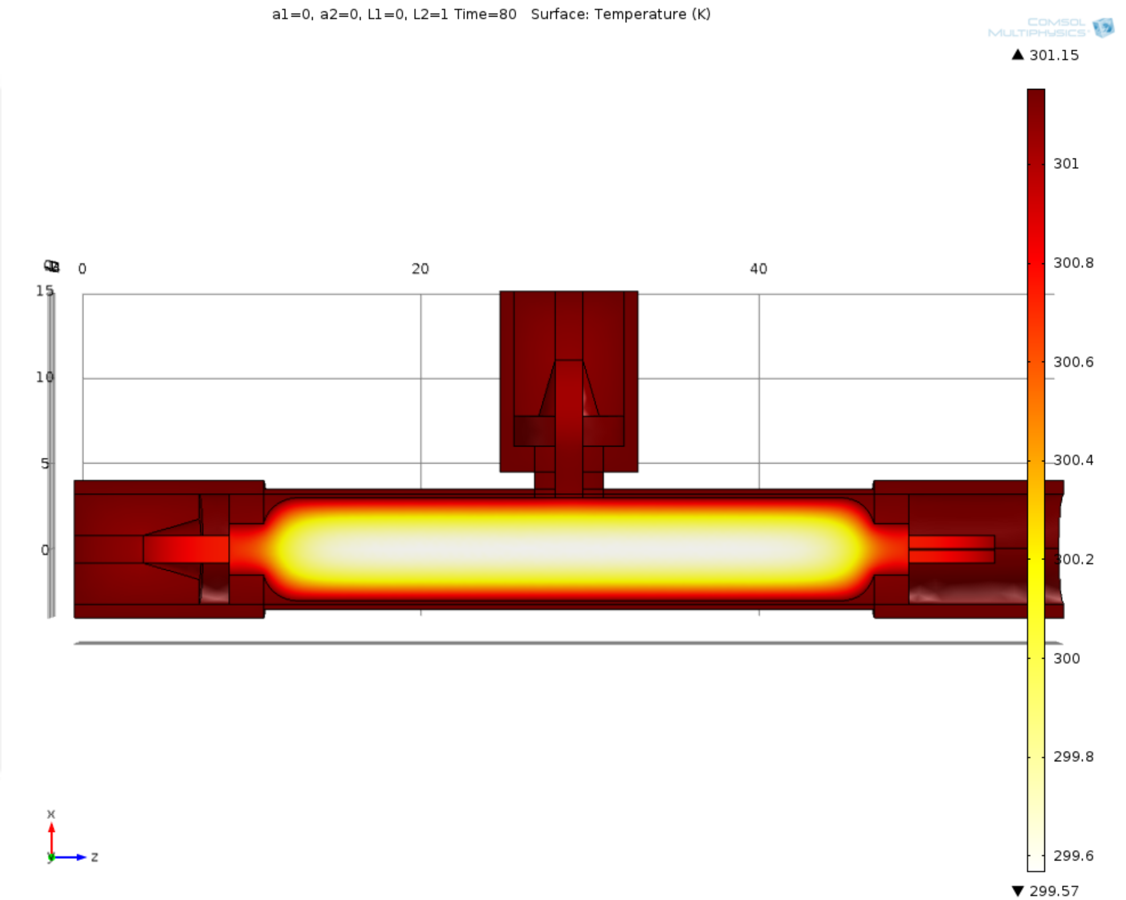
# Corrections

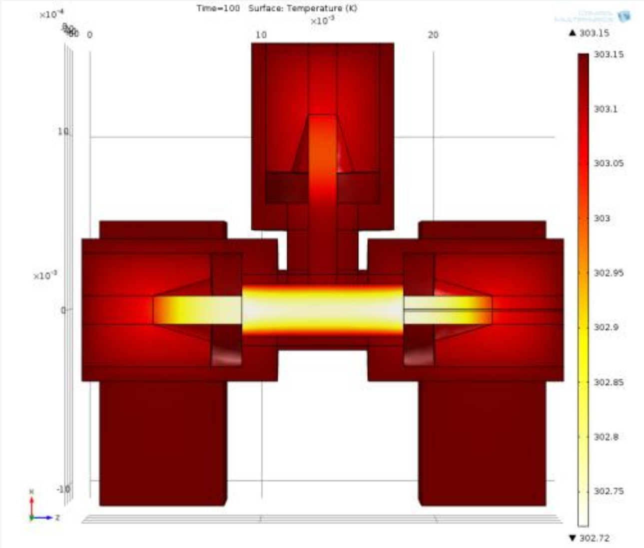
*Cooling down of fluid elements*



# Corrections

## *Spatial temperature gradient – impact volume*



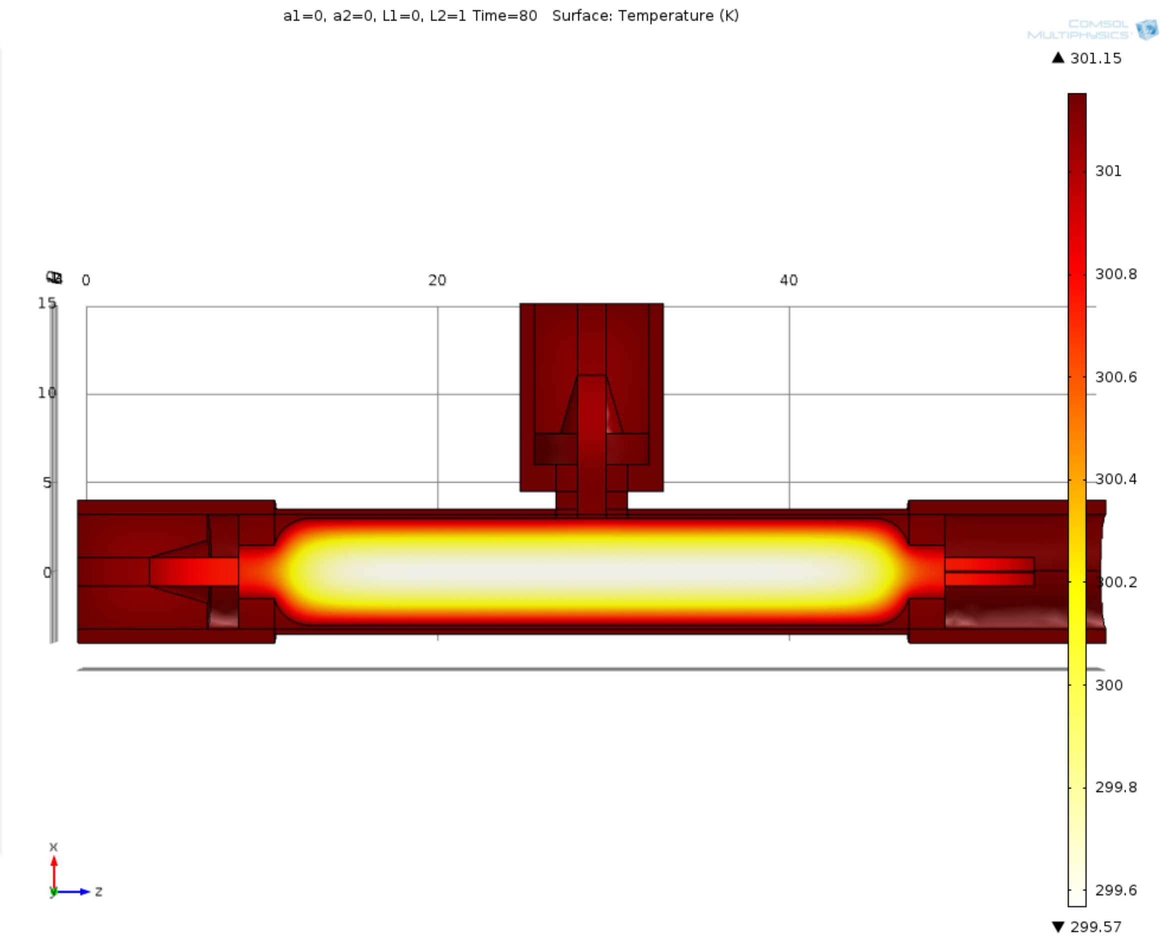




V = 1000 mm$^3$

V = 63 mm$^3$

# Corrections

*Spatial temperature gradient – impact gradient*




Temperature gradient is 0.01 K/s

Temperature gradient is 0.1 K/s

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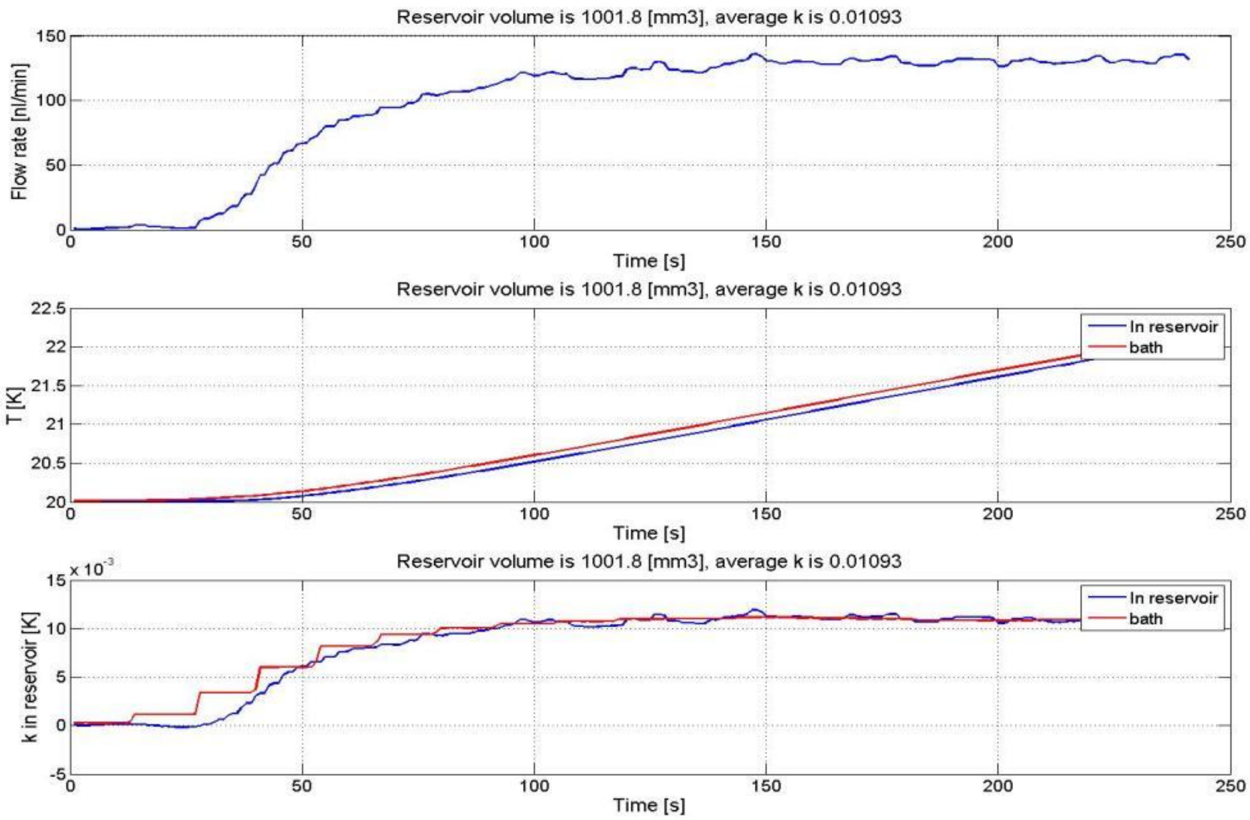
# Preliminary results

*Flow rate for k = 0.01 K/s, reservoir vol 1000 mm³*



# Outlook

- Finish primary standard (August)
- Comparison between primary standards (starting September)

- Metrological assessment drug delivery devices
- Metrological assessment flow meters
- Best practice guide line

- Other applications
  - High performance Liquid Chromatography (HPLC)
  - Lab-on-a-chip (?)
  - ?

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VSL

# Thank you for your attention!

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