Calibration services for health care

Hugo Bissig METAS, Elsa Batista IPQ,
Peter Lucas VSL, Harm Tido Petter VSL,
Anders Koustrup Niemann DTI,
Florestan Ogheard CETIAT,
Martin Ahrens FH Lübeck

MEDD
Drugmetrology.com

Content

- Metrology for Drug Delivery - Overview
- 3 types of primary standards for calibration
  - Gravimetric method
  - Water front tracking in a capillary
  - Liquid thermometer method
- Validation of primary standards by means of inter comparison

Motivation Metrology for drug delivery (MeDD)

1. IV therapy *can* cause adverse patient incidents (various (inter)national studies)
2. Wide spread usage of infusion
3. Characteristics of infusion pumps + accessories not fully known
4. Un(der)developed and underused infrastructure for (low) liquid flow rate calibrations

Unknown characteristics
Reduced accuracy in delivered doses

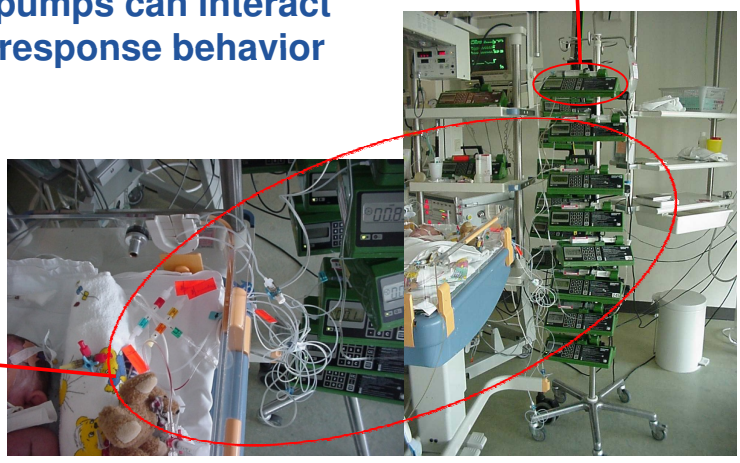
Typically only the infusion pump (plus syringe) is 'calibrated' (according to existing written standards)

Adding accessories changes the response time

For a multi-pump set up, the pumps can interact with each other affecting the response behavior

Well characterized

Hardly characterized



What has MeDD delivered?

1. **Metrology: upgraded and validated infrastructure for flow rate calibrations from 600 ml/h down to 0.006 ml/h**
2. **System characteristics: show cases infusion pump set ups**
   - Pump plus accessories: effective flow rate, stability and start up time (compliance)
   - Dependency on fluid and process parameters (temperature, viscosity, flow rate, …)
3. **Knowledge and awareness: best practice guide and input to current written standards**

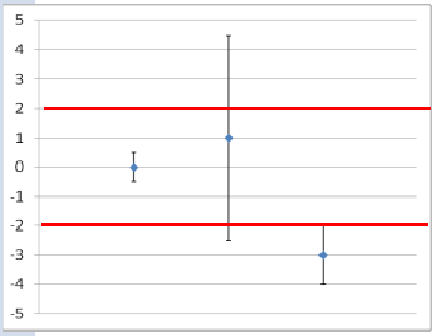
MeDD *Consortium*

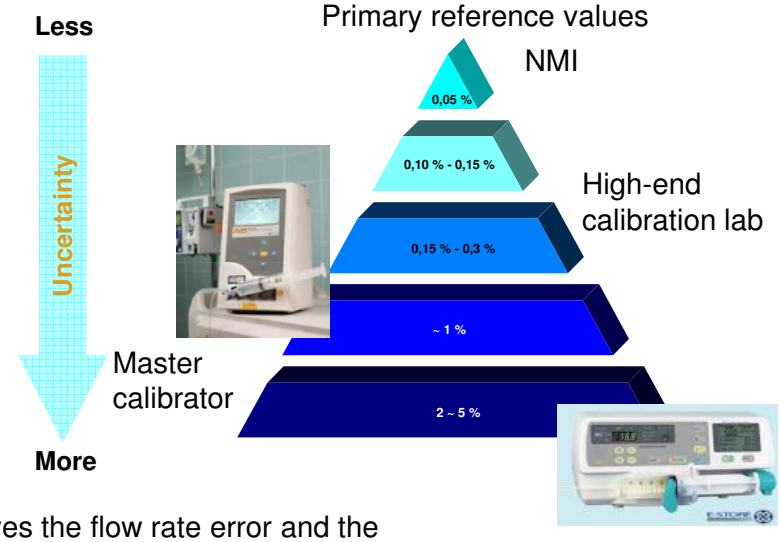
1. **National Metrology institutes: VSL (NL), CETIAT (FR), CMI (CZ), DTI (DK), IPQ (PT), METAS (CH), UME (TR)**
2. **University Medical Centre Utrecht (NL)**
3. **Lübeck University of Applied Sciences (DE)**
4. **EMRP Grant (2012, Health call)**
   - Metrology-focused European programme
   - Accelerate innovation and competitiveness in Europe whilst continuing to provide essential support to underpin the quality of our lives

www.drugmetrology.com

Why calibraton? Why traceability to SI-Units?

Uncertainty of calibration has to be 3 (5) times smaller than the stated accuracy of the device under test or the maximum permissible error





- A sound calibration gives the flow rate error and the uncertainty in that error
- Traceability is a guarantee for quality of calibration results

3 Types of Primary Standards

Gravimetric method

Flow rates
100 nl/min – 10 ml/min

VSL Dutch Metrology Institute
CETIAT ensemble, innover et valider
Instituto Português da Qualidade – Ministério da Economia e do Emprego
Danish Technological Institute
METAS

Water front tracking in capillary

Flow rates
5 nl/min – 1 µl/min

Fachhochschule Lübeck University of Applied Sciences

Liquid thermometer method

Flow rates
30 nl/min – 1.5 µl/min

VSL Dutch Metrology Institute

3 Types of Primary Standards

Gravimetric method

Flow rates
100 nl/min – 10 ml/min

Water front tracking in capillary

Flow rates
5 nl/min – 1 µl/min

Liquid thermometer method

Flow rates
30 nl/min – 1.5 µl/min

Water droplet

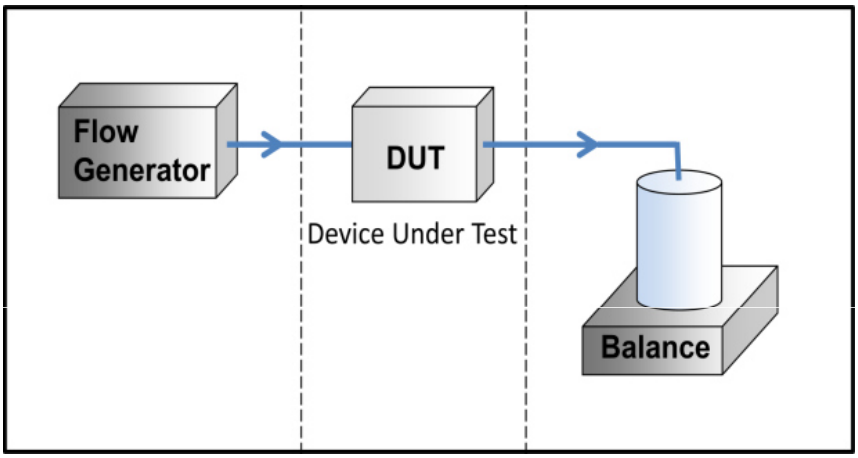
Size 50µl
(Pharmacology, Wikipedia)

Flow rate **10 ml/min**,
time to get the droplet: **0.3 s**

Flow rate **100 nl/min**,
500 min (8h 20 min)
working day in Switzerland

Flow rate **5 nl/min**,
Full week (24/7)

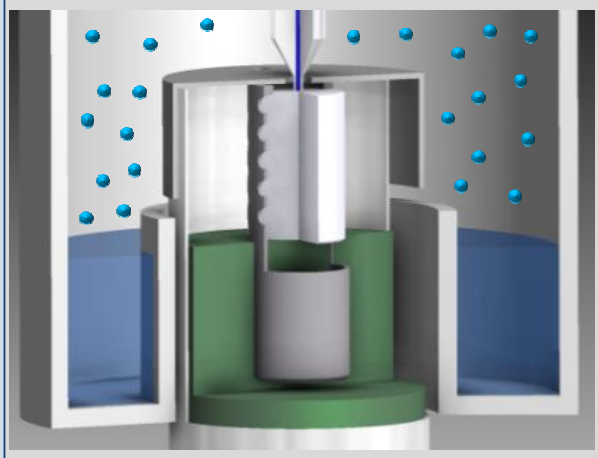
Gravimetric Method



- 2 types of collecting water in beaker to avoid droplet formation and minimize evaporation
- 2 principles for flow generator

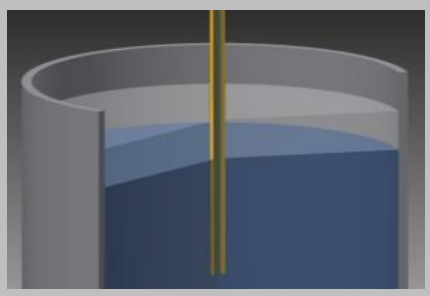
2 types of collecting water in beaker to avoid droplet formation and minimize evaporation

Water Bridge to waterabsorbing materials in saturated air

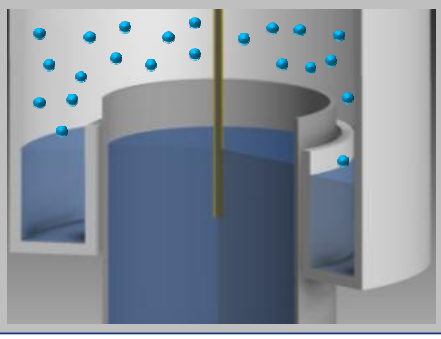


Needle immersed into water

- **with oil cover**

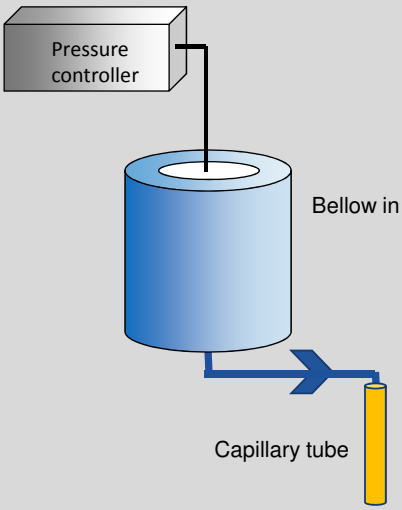


- **in saturated air**



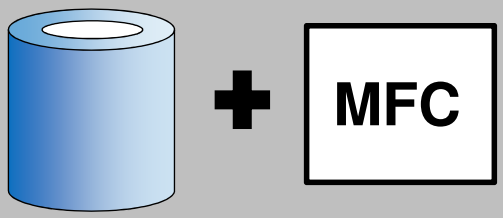
Flow Generator: 2 principles

Constant pressure drop over capillary tube setting the flow rate

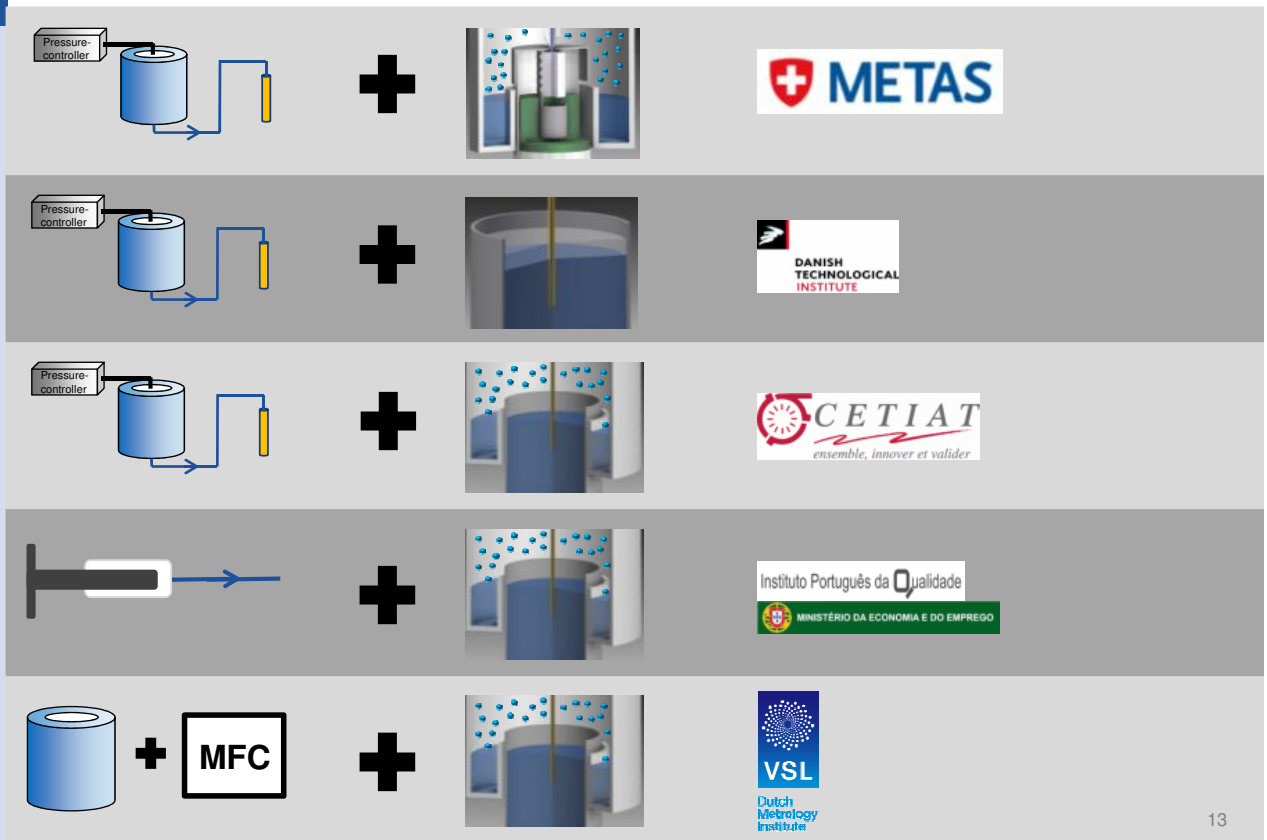


Syringe pump setting the flow rate

MFC setting the flow rate

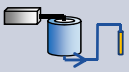
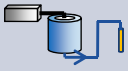
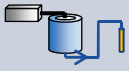
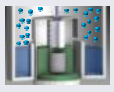
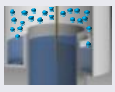
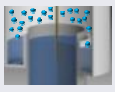


Flow generator and water collection method



Micro Flow Facility – Gravimetric setup

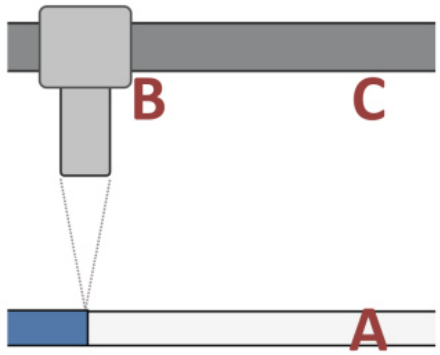
Characteristics

	METAS	DTI	CETIAT	IPQ	VSL
Flow rate range	1 ml/min – 100 nl/min	16 ml/min – 100 nl/min	133 ml/min - 16 µl/min	10 ml/min - 50 nl/min	16 ml/min - 4.2 µl/min
Uncertainty (k = 2)	0.1 - 0.6 %	0.05 - 0.6 %	0.04 – 1 %	0.15 - 6 %	0.06 - 1.4 %
Water temperature	Ambient	Ambient	10 - 50 °C	Ambient	Ambient
Pressure range upstream DUT	0 – 2.5 bar	0 – 5 bar	0 – 10 bar	0 – 2 bar	0 – 5 bar
Flow generator					
Water collection					

Biomedical Engineering / Biomedizinische Technik. Band 60, Heft 4, Seiten 301–316

Water front tracking in a capillary

Measurement priciple: front tracking system

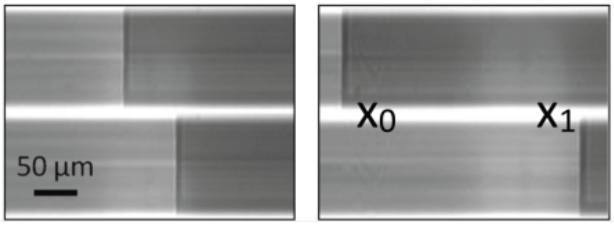


$x_1 - x_0$: traveling distance

$t_1 - t_0$: measurement time

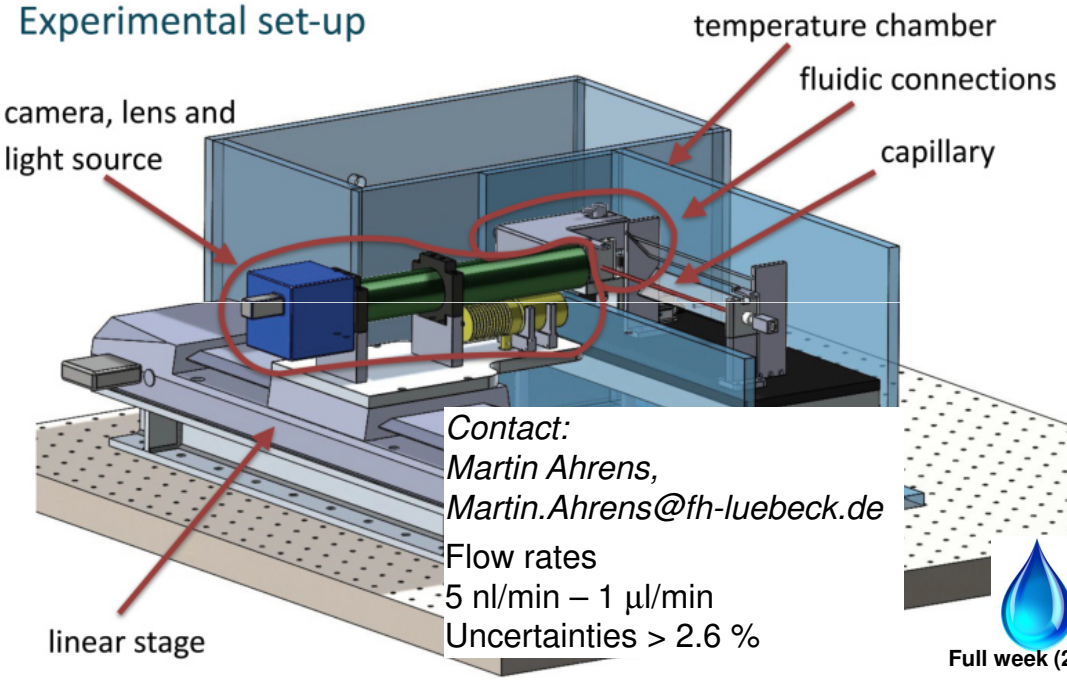
R: radius of the capillary

$$\dot{V} = \frac{dV}{dt} = \frac{x_1 - x_0}{t_1 - t_0} \cdot \pi \cdot R^2$$



Water front tracking in a capillary

Experimental set-up



Contact:
Martin Ahrens,
Martin.Ahrens@fh-luebeck.de

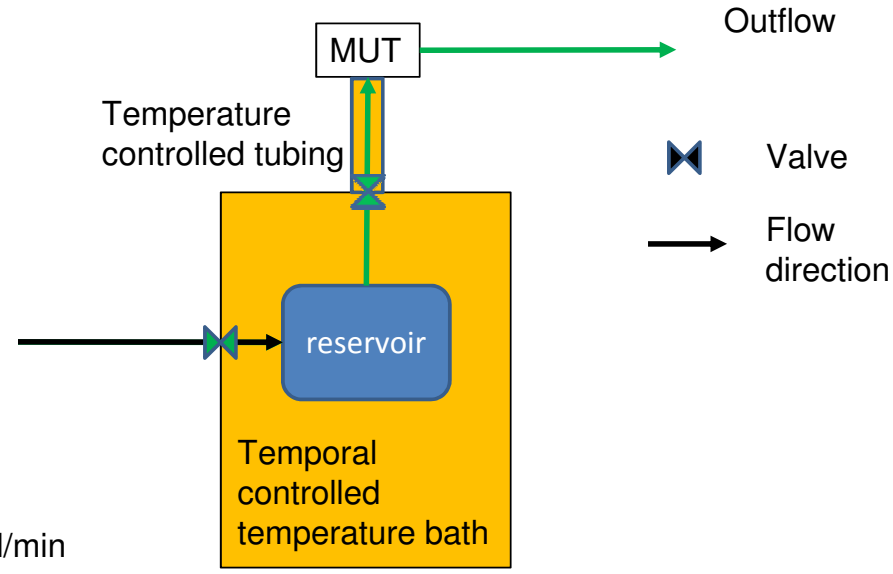
Flow rates
5 nl/min – 1 µl/min
Uncertainties > 2.6 %

Full week (24/7)

Biomedical Engineering / Biomedizinische Technik, Band 60, Heft 4. Seiten 337-345

Primary standard for nanoflow rates

Working principle



Contact:
Peter Lucas,
PLucas@vsl.nl

Flow rates

30 nl/min – 1.5 µl/min

Uncertainties: 3.0 % - 2.5 %

Biomedical Engineering / Biomedizinische Technik, Band 60, Heft 4. Seiten 317-335

Validation of primary standards by means of inter comparison

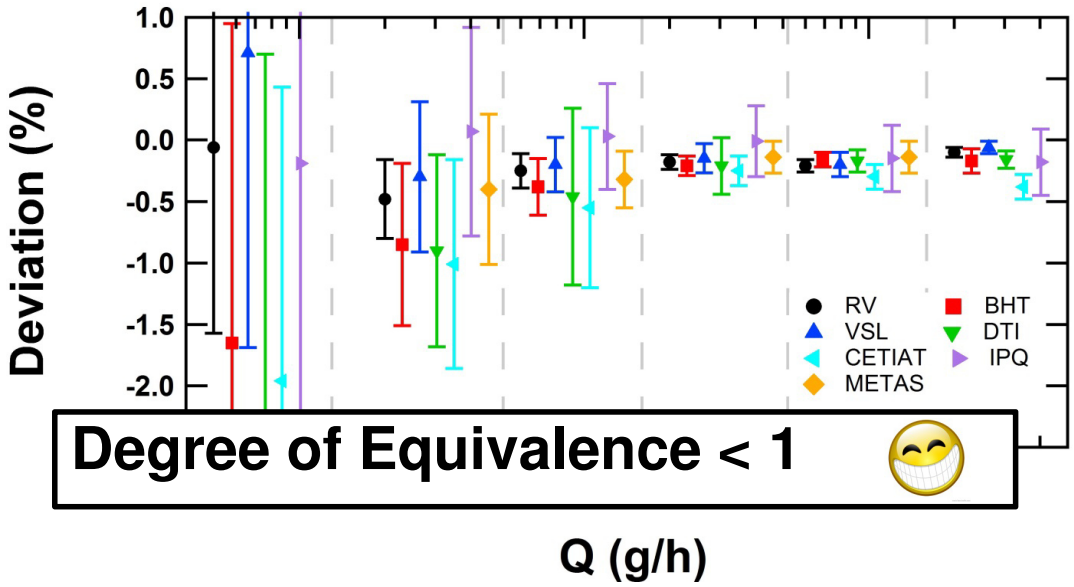
EURAMET project 1291 / EURAMET.M.FF-S7
« Comparison of primary standards for liquid micro flow rates »

Internal report of MeDD (D 2.3.4)
« Comparison of primary standards for liquid nano flow rates »

Validation of primary standards by means of inter comparison

EURAMET project 1291 / EURAMET.M.FF-S7

« Comparison of primary standards for liquid micro flow rates »



Micro Flow Facility – metrological infrastructure for low flow rate testing

Testing and calibration of

- Flow meters
- Flow generators
  - Syringe pump
  - Peristaltic pump
  - Insulin pump

Within this infrastructure it is possible to perform calibrations for different viscosities, temperatures and back pressure.

Micro Flow Facility - Contacts

Gravimetric setup

Flow rates
100 nl/min – 10 ml/min

Hugo Bissig
Hugo.Bissig@metas.ch

Florestan Ogheard
florestan.ogheard@cetiat.fr

Elsa Batista
ebatista@ipq.pt

Anders Koustrup Niemann
aknn@teknologisk.dk

Harm Tido Petter
HPetter@vsl.nl

Liquid thermometer method

Flow rates
5 nl/min – 1 µl/min

Peter Lucas
PLucas@vsl.nl

Water Front Tracking

Flow rates
30 nl/min – 1.5 µl/min

Martin Ahrens,
Martin.Ahrens@fh-luebeck.de

Questions ?