METROLOGY for DRUG DELIVERY

Designing a multi infusion setup

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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

Outline

- Setting the Scene: the Need for this Research
- Former Projects
- The Goal
- What is Multi-infusion?
- Medication Therapy and Goals of Infusion
- Common Characteristics of Todays Systems and Infusion Components
- Component procurement and Development of a Test Matrix
- Designing the system: process and pitfalls
- Conclusions

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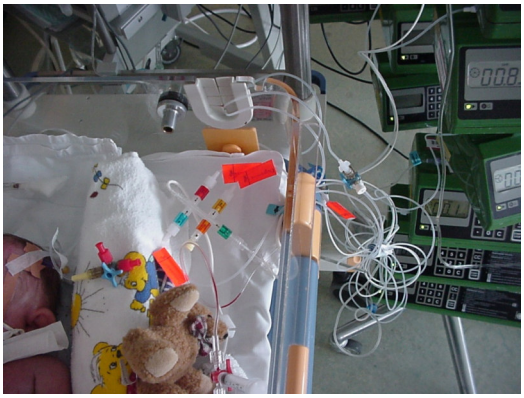
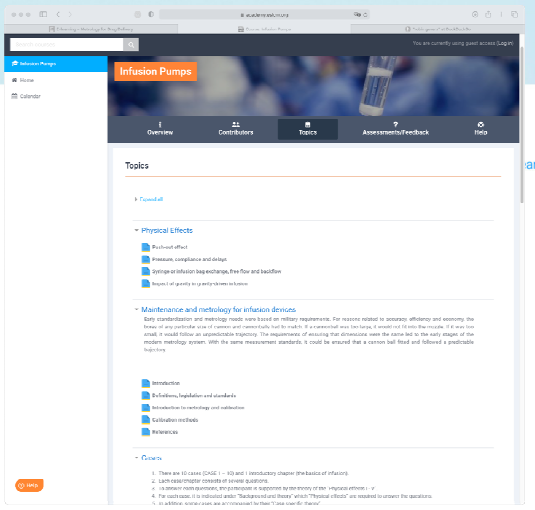
Background: How I was drawn to infusion



Rotterdam, Erasmus MC 2001

- Infant with acute blood pressure problem
- Dopamine infused to raise blood pressure
- No result
- Increasing dopamine flow rate
- No result
- Increasing dopamine again
- Overshoot
- No relation found with dopamine setpoint
- Decreasing dopamine flow rate
- No result
- Etc..



an Metrology Research Programme), started in 2012.

The initial joint research project aimed to develop:

- traceable calibration services for drug delivery systems for flow rates down to 1 nl/min transfer standards for onsite calibration
- assessment of the drug delivery devices
- a best practice guide for drug delivery

The European Society of Intensive Care Medicine (ESICM) in close cooperation with an EMPIR Consortium from IPQ, VSL and UMC Utrecht upgraded the e-learning with interactive components and animations.

Cases from clinical practice and calibration and maintenance were included

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The goal

To design and develop a multi-infusion system containing check valves, with several options for testing how liquids, with different viscosities mix and flow and how this affects drug concentration. The flow rates and pressures will be traceably calibrated in all infusion lines, as well as at the outlet of the syringe pump, to be able to analyse the effects of pressure-equalising devices and to detect occlusion phenomena and bad mixing configurations.

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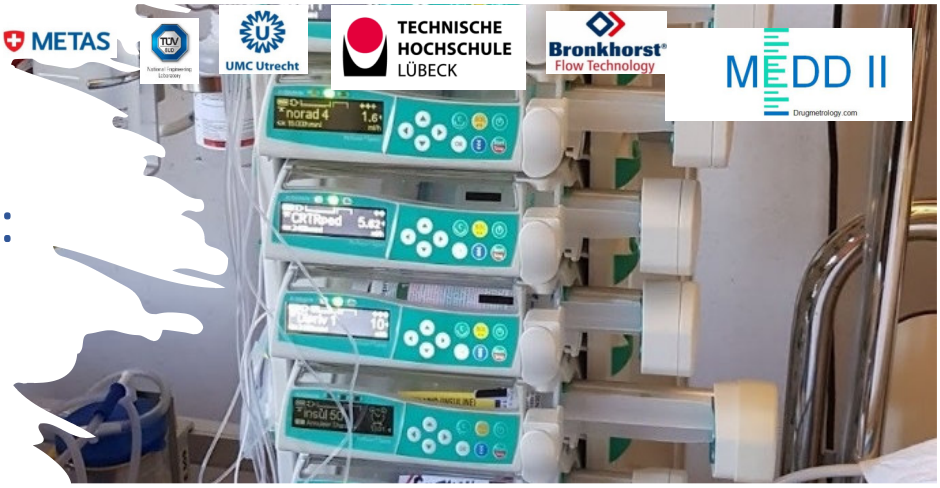
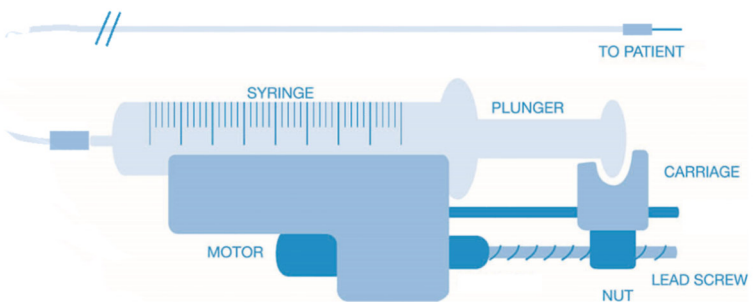
Designing a Multi-Infusion Setup:

- Clinician Interviews
- Manufacturer and Technician Interviews
- List of Components
- Design a Test Matrix





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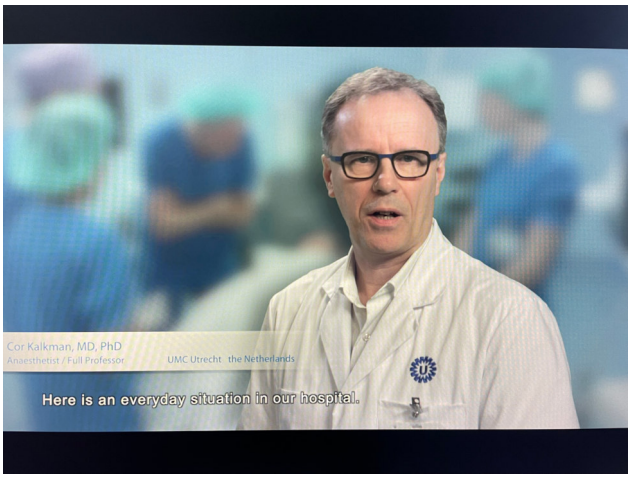
Clinical situations: transporting a patient



[Infusion Pumps: Blood pressure management of a patient during and after surgery. (esicm.org)]

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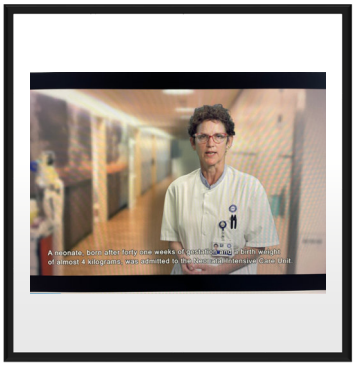
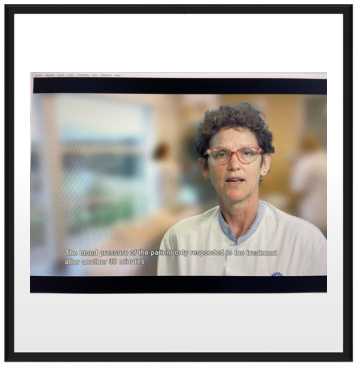
TECHNISCHE HOCHSCHULE LÜBECK

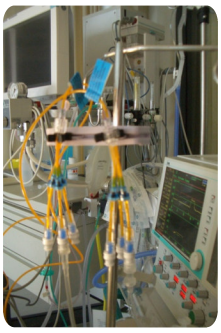


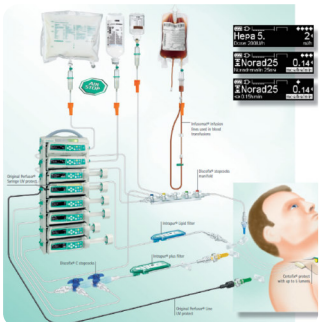


TECHNISCHE HOCHSCHULE LÜBECK

What are we talking about?

- Almost every patient receives medication therapy via infusion
- Many different applications
- Many users
- Many mistakes
- Of which some of high impact





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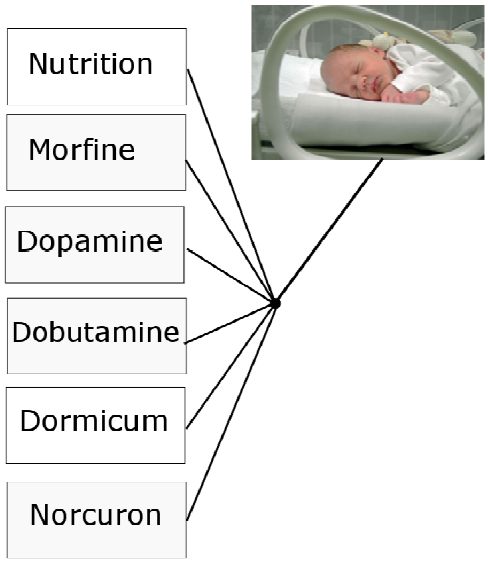
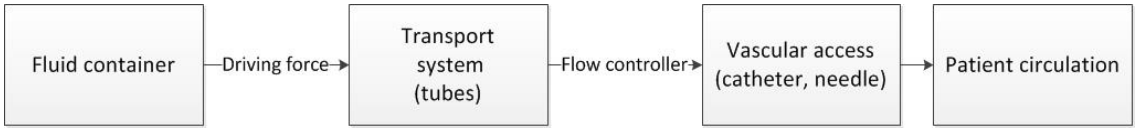
What is multi-infusion?

- Administer drugs directly into vein patient
  - Fast
  - Continuous
- More than one drug administered at the same time over one line: multi-infusion
- This happens often for neonates



Infusion schedule



Fluid containers:
- Bags
- Flasks
- Syringes

Driving forces:
- Gravity
- Positive displacement

Flow controllers:
- Drip chamber/ clamp: counting droplets
- Calibrated step motor

Vascular access
- Catheters and needles

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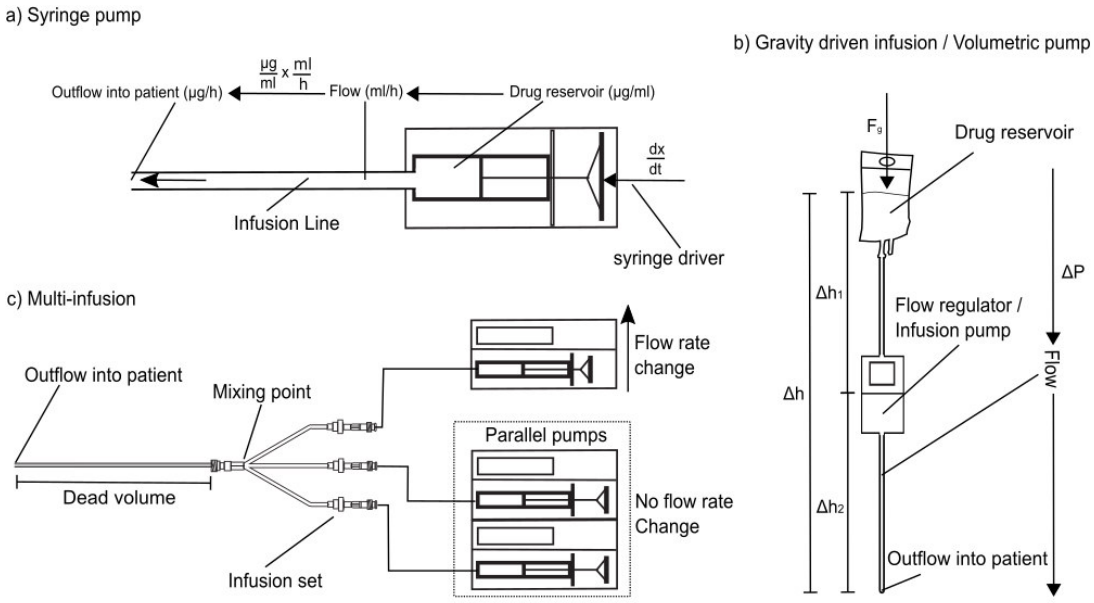
Infusion setups



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R.A. Snijder: **Physical causes of dosing errors in patients receiving multi-infusion therapy, PhD Thesis, 2016**

Component Procurement and Development of Test Matrix

Goal: select effective components and establish test protocols mimicing realistic multi-infusion scenarios

- Survey clinicians on what is clinically relevant
- Focus on at least 4 known high impact issues
  - multiple viscosities, air bubbles, and occlusion alarms.
- What does the clinical environment look like?
- Define a test matrix
  - Use real medication
  - Select components

Task 4.1.1

UMCU and THL will conduct a literature review and a minimum of 5 clinician interviews in order to obtain a comprehensive overview of clinical best practice for drug delivery using multi-infusion systems.

Task 4.1.2

Using input from A4.1.1, UMCU and THL will identify and prepare a list of the components that will be required to prepare a clinically realistic setup for a multi-infusion drug delivery system.

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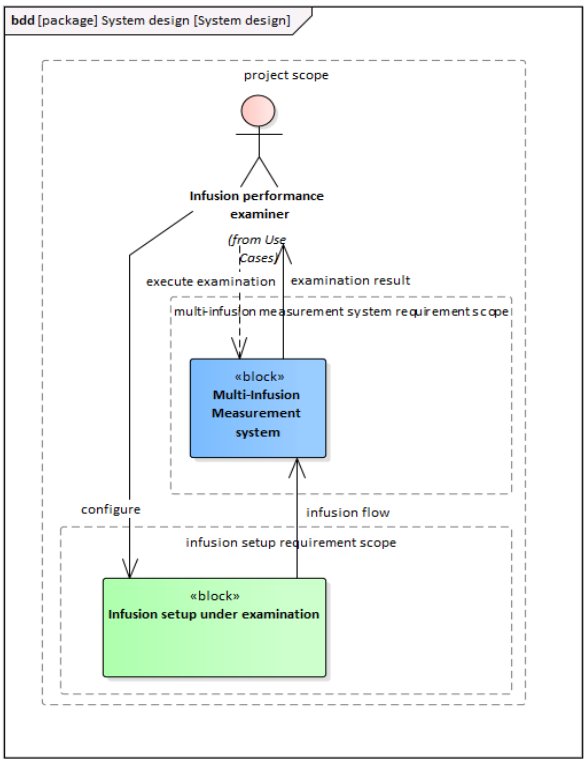
Designing a multi-infusion setup

- Design step: separate
  - Infusion setup under examination (use cases)
  - Multi-infusion measurement system
  - Different criteria for each part
- Setup under examination:
  - Clinical relevance most important
  - 3 setups chosen in accordance with clinician interviews
- Measurement setup:
  - Most important: both
    - Equivalence to clinical situation and
    - Stable measurement conditions



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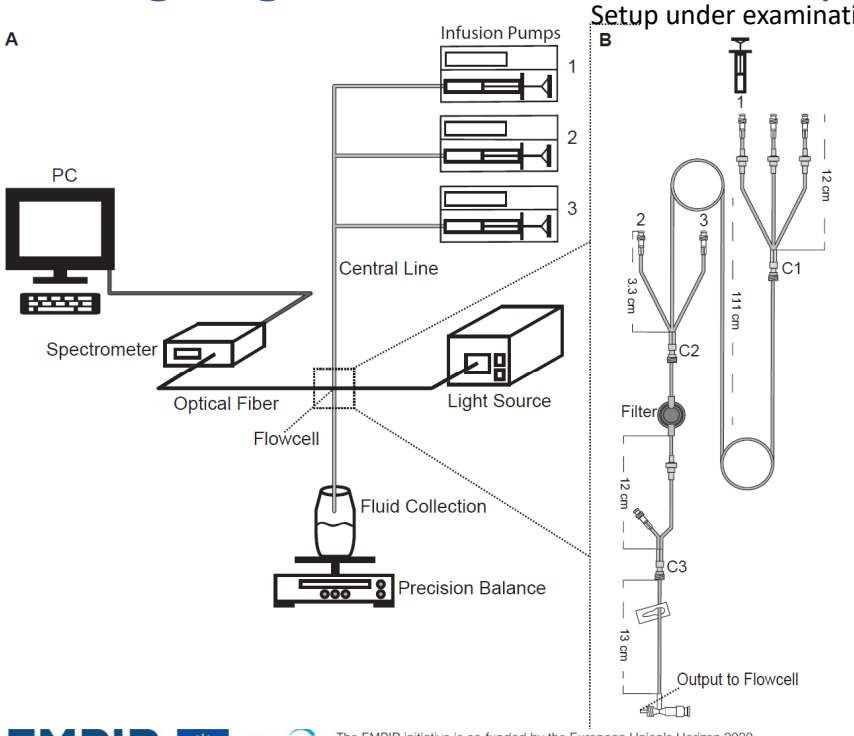
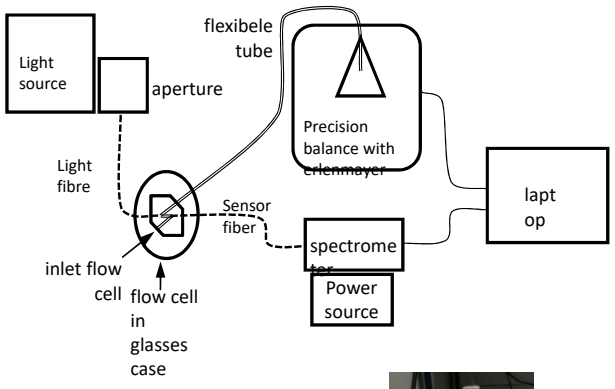
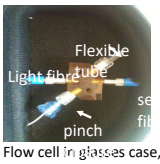
Designing a multi-infusion setup: MeDD I

Setup under examination

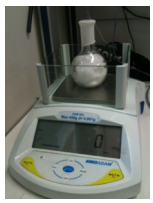


Measurement System





Flow cell in glasses case, with pinch closure and light and sensor fiber



Precision balance with conical flask with gauze pads and glove

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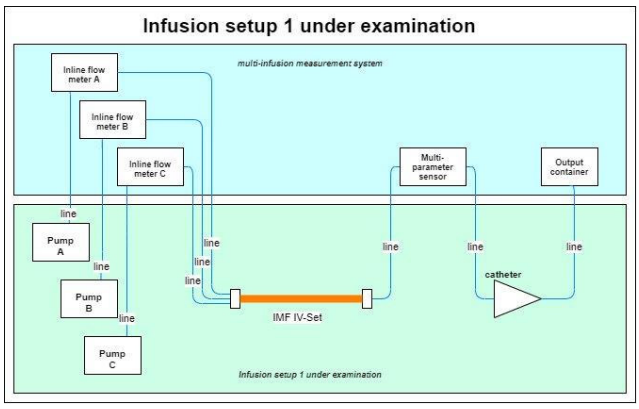
Designing a multi-infusion setup – A complex process

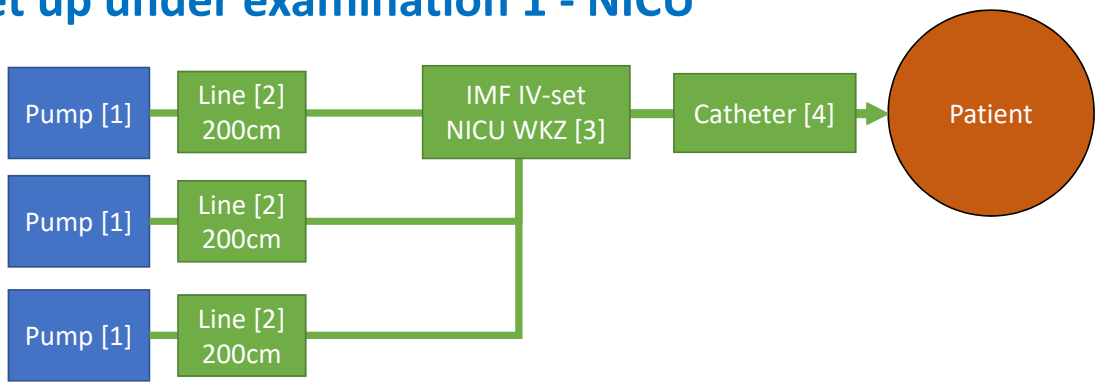
- Clinical practice: Many different components are used
- MeDD I setup: uses laser dyes, not real drugs
- Covid-19 and Brexit: limited availability of certain components
- Pragmatic response: use available components and act flexible, within clinical practice



Asked Component description	Quantity
B.Braun Omnifix 50ml Syringe REF4617509F	20
Syringe driver extension tubing for photosensitive products . O 1 x 2,5mm- Opaque syringe cover included, 200 cm, 1,6 ml. (Cair LGL).	6
MF IV-set Neo WKZ 1mm inner diameter and 1.68 meter; check valve and filter (15 ƒÊm fluid filter) included in the set.	2
Vygon, Premi cath REF1261.20, 28 G (1fr), 20 cm, PUR.	2
Original Perfusor Line BBraun, PVC, 150 cm, 1.5 x 2.7, 2.9 ml.	16
BBraun Discofix C 3-gang manifold. REF16600C	2
A filter in the second line from the mixing point to the patient.	2
Catheter type: Vygon, Peripherally inserted central venous catheter REF1254.30, inner diameter 0.8 mm, outer diameter 1.3 mm, 30 cm, PUR, 4 Fr.	2
Vygon Vystar female / male of five 3-way stopcocks. REF5827.95	2
Vygon, Paediatric Multicath 2, double-lumen, central venous catheter REF1203.202, inner diameter 1.5 mm, outer diameter 4.5 mm, 20 cm, PUR.	2

Designing a multi-infusion setup example

Set up under examination 1 - NICU



[1] Pumps with 50 mL syringes
[2] Line type: Syringe driver extension tubing for photosensitive products – Ø 1x2,5mm – Opaque syringe cover included 200cm, 1,6 mL (Cair CGL)
[3] Set type: IMF IV-set Neo WKZ 1mm inner diameter and 1.68 meter; check valve and filter (15µm fluid filter) included in the set
[4] Catheter type: Vygon, Premi cath 1261.20, 28 G (1fr), 20 cm PUR

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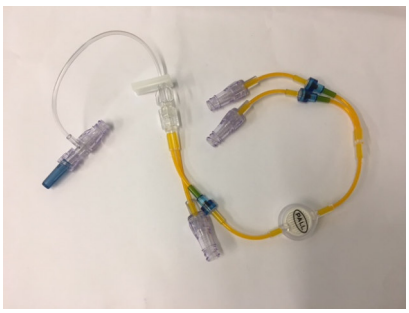
Designing a multi-infusion setup example

Set up under examination 1 – NICU components

Line [2]

IMF IV-set NICU WKZ [3]



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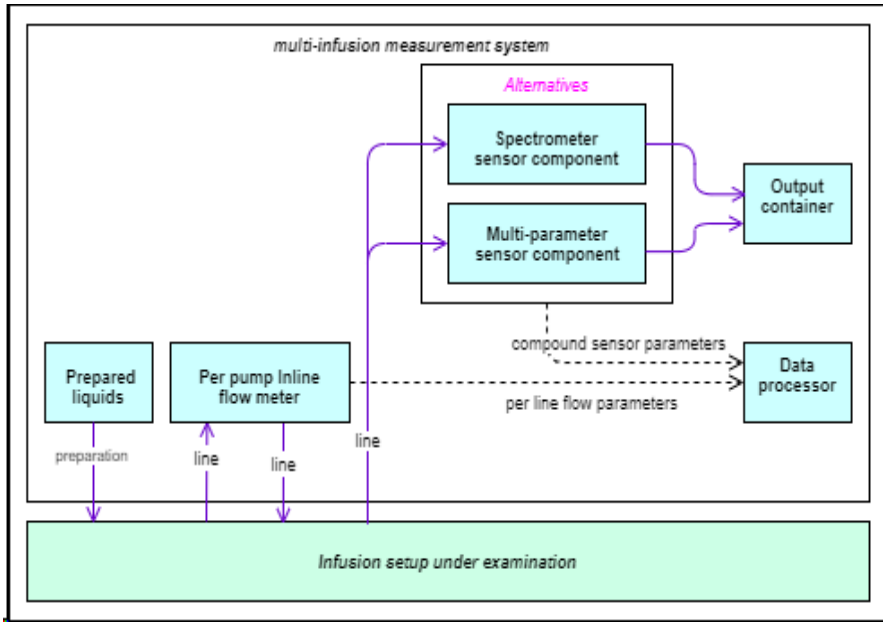
Designing a multi-infusion setup example



Current Challenges

- Components of infusion setup under examination not always available or in stock. This got worse during Covid. Impediment to use always same components and assessing component characteristics
- ➢ Mitigation: task division between partners of the setups to test.
- MIMS components can influence the flow in the setup under examination making it less realistic
- ➢ Make the best of both worlds: Compare laser dye setup vs MEMS setup

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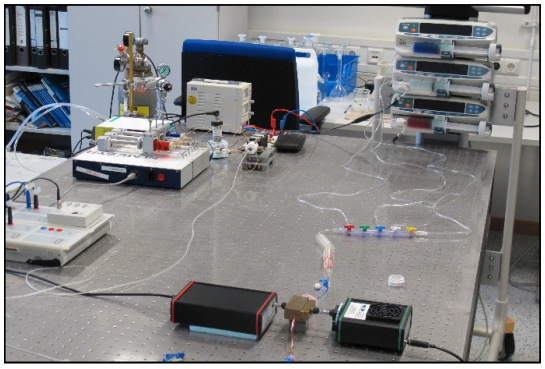
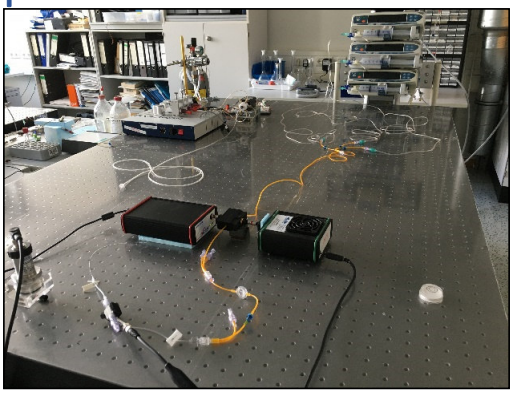
Designing a multi-infusion setup

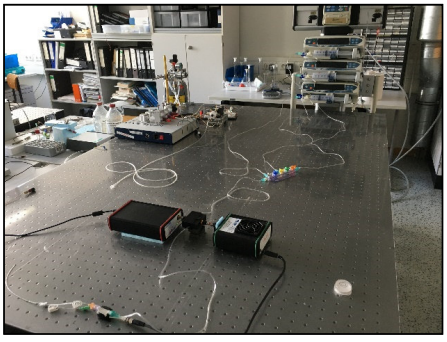




Setup 1

Global setup with infusion lines from Lübeck

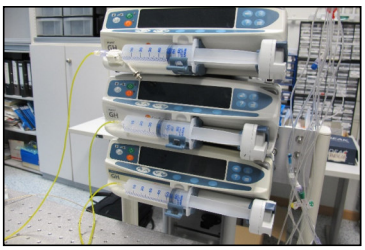
Setup 2 /NA. Eliminated in Lübeck



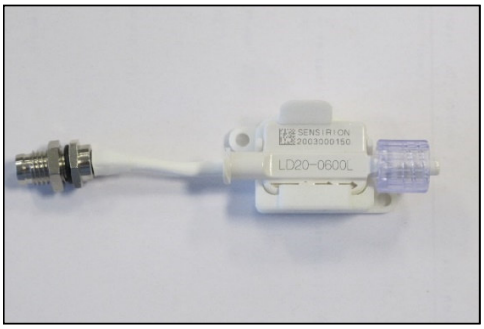
Setup 3

Designing a multi-infusion setup

Integration of sensors: Lübeck



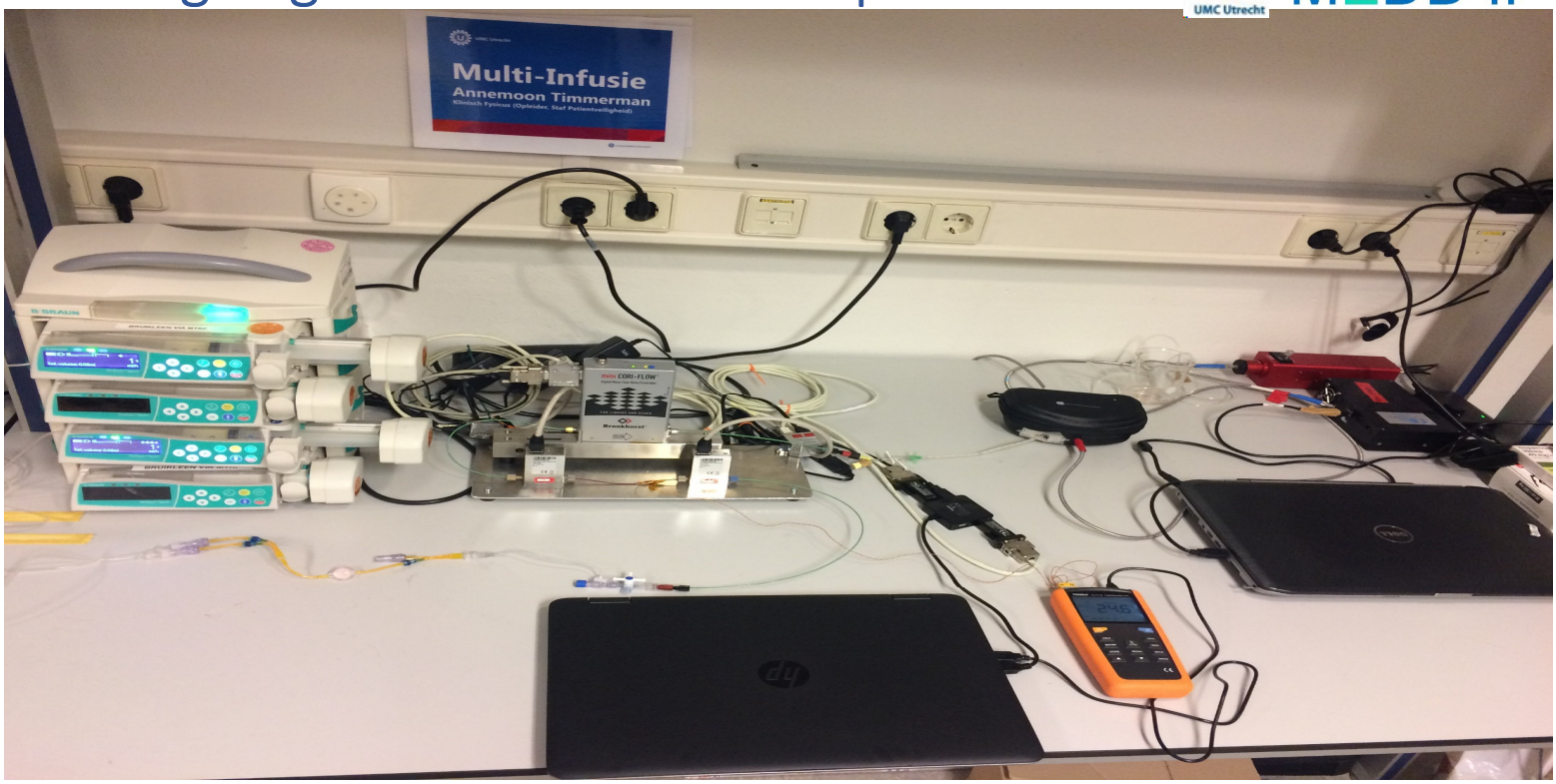
Syringe pumps with flow sensors



Flow sensor (Sensirion)
with its holder

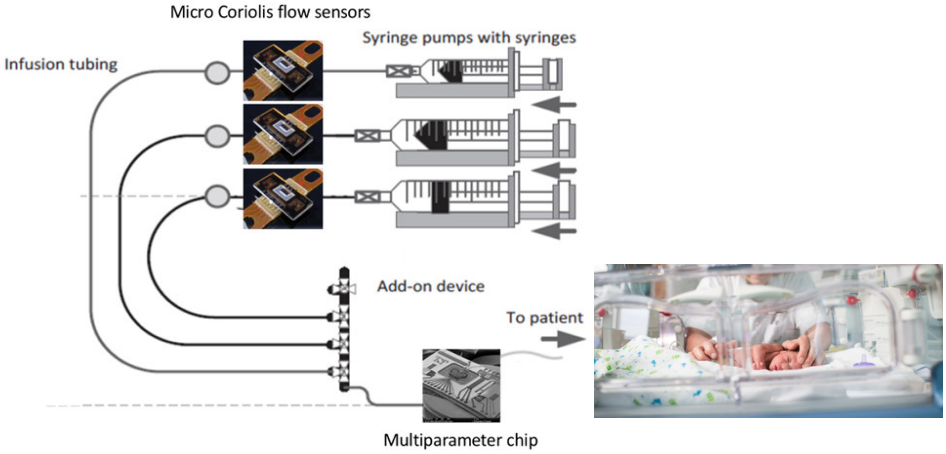
Pressure sensors (WIKA).
To be replaced with luer
sensors (elveflow)

Designing a multi-infusion setup - Utrecht



Designing a multi-infusion setup

Integration of sensors



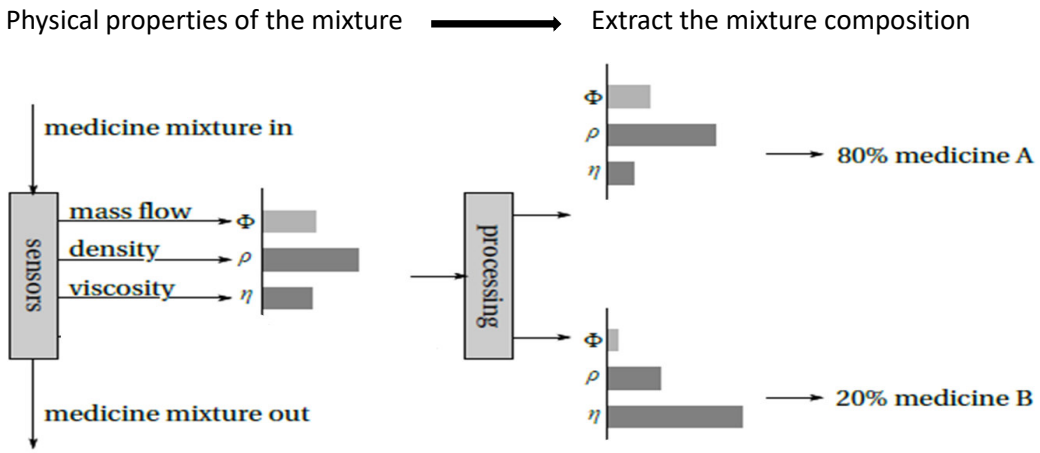
(1) Measure flow and pressure at the output of each infusion pump in multi-infusion systems
(2) Coriolis measurement principle is independent of the type of drug or drug mixture
(3) Measure flow and medicine mixture composition where the drug enters the patient
(4) Feedback information to the pumps to adjust the flow rate (manually / controlled)

Designing a multi-infusion setup

Integration of sensors

Measuring the composition, in order to improve multi-infusion, indirectly by measuring the fluid physical parameters such as density and viscosity, as illustrated below.

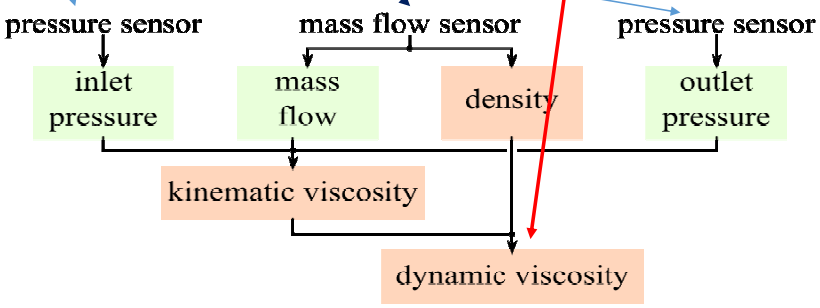
When it is known which liquids are in the mixture (with known parameters each), the concentration of those liquids can be obtained assuming the mixing has a linear scaling effect.



Designing a multi-infusion setup
Integration of sensors

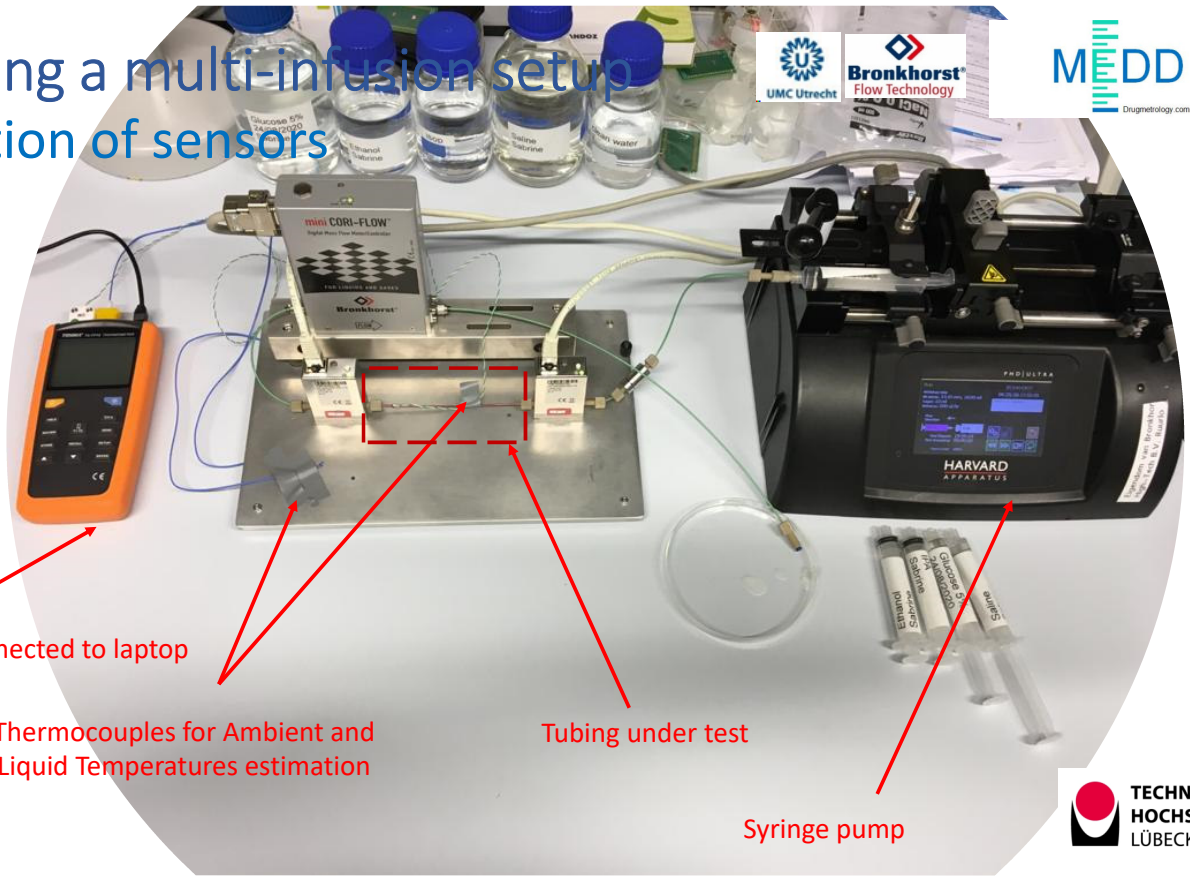
Due to low velocities of medicine administration, the flow is laminar, which means that the pressure drop inside of the circular tubing is a function of the volumetric flow rate and the fluid's viscosity. As seen in the Hagen-Poiseuille equation expressed below:

$$\Delta P = \frac{8\mu L Q}{\pi R^4} \qquad \mu = \frac{\Delta P \pi R^4}{8LQ}$$



Based on this equation, we placed 2 pressure sensors upstream and downstream of a tube with 100 µm internal diameter. As well as a mass flow sensor. This allows for the measurement of flow and pressure drop and by extension the estimation of dynamic viscosity.

Designing a multi-infusion setup
Integration of sensors



Designing a multi-infusion setup
Integration of sensors

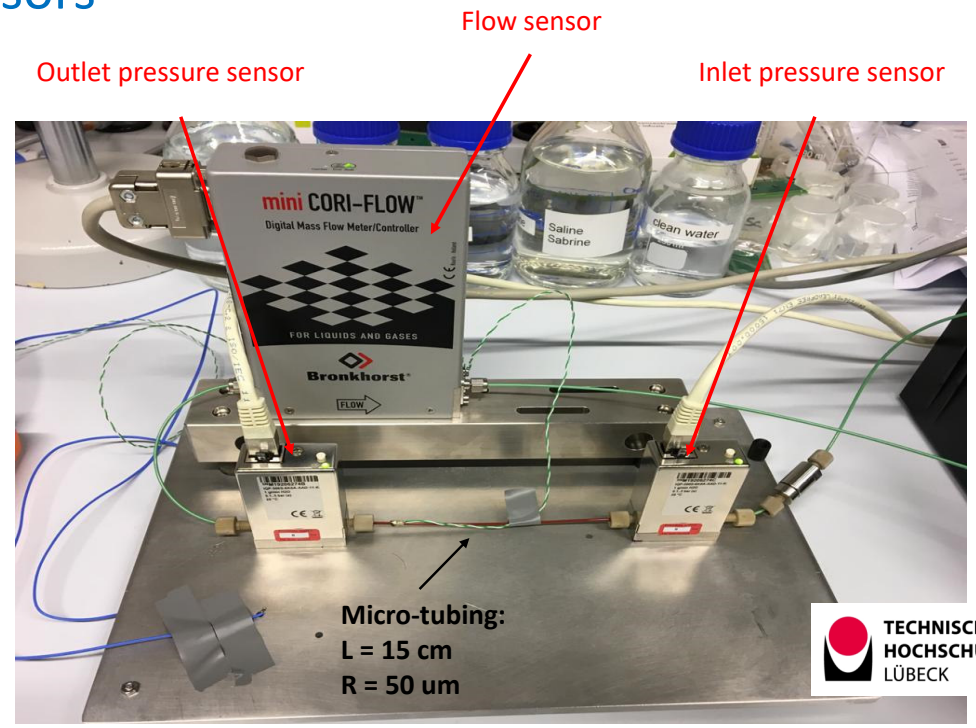
Equipment properties:
- MiniCori Flow

Max mass flow: 1g/h
- Pressures sensors

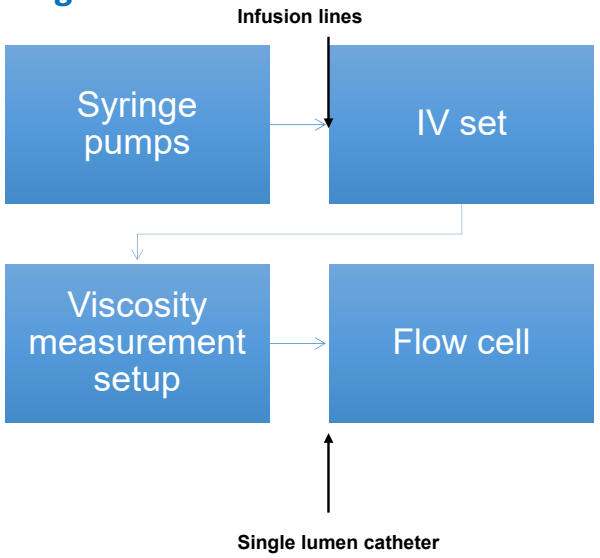
Max pressure: 5 bar
- Syringe pump

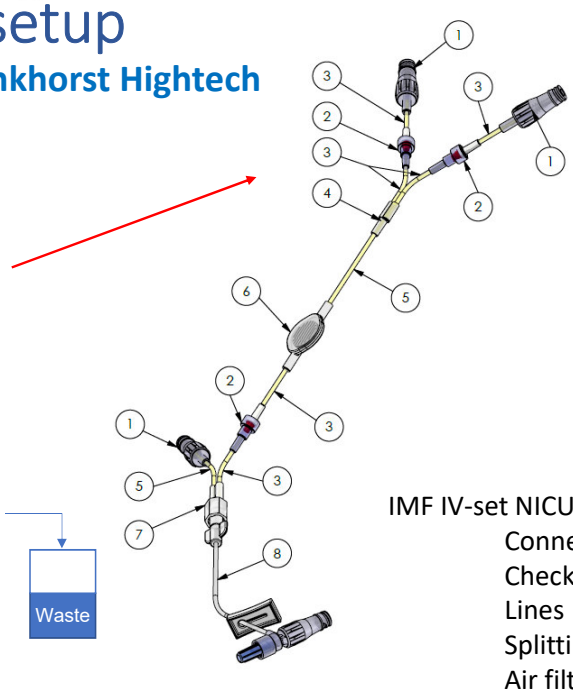
Applied flow rate 5 ml/h
- Peeksil tubing

Internal diameter 100 µm



Designing a multi-infusion setup
Integration of sensors: UMC Utrecht & Bronkhorst Hightech

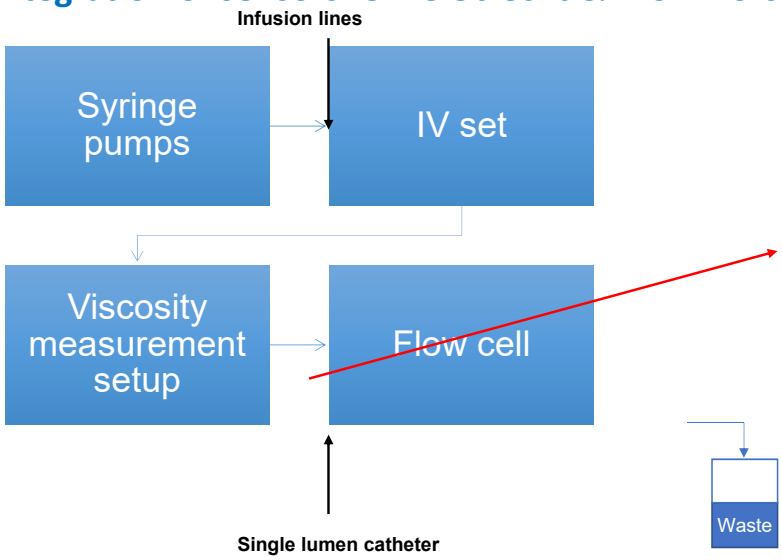


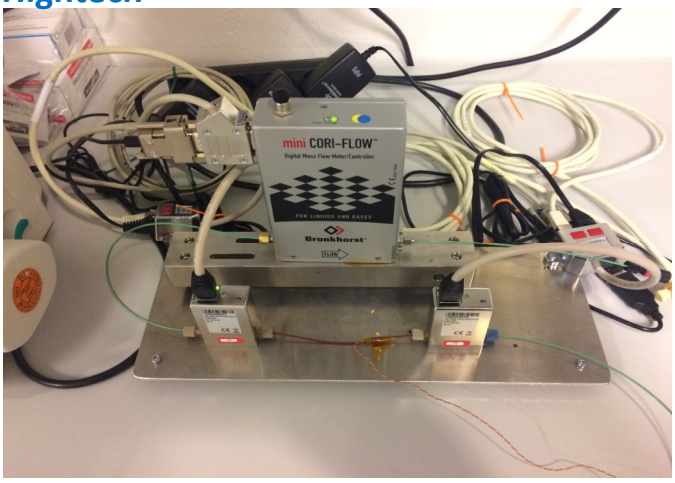


IMF IV-set NICU WKZ
- Connectors [1]
- Check-valves [2]
- Lines [3,5,8]
- Splitting point [4,7]
- Air filter [6]

Designing a multi-infusion setup

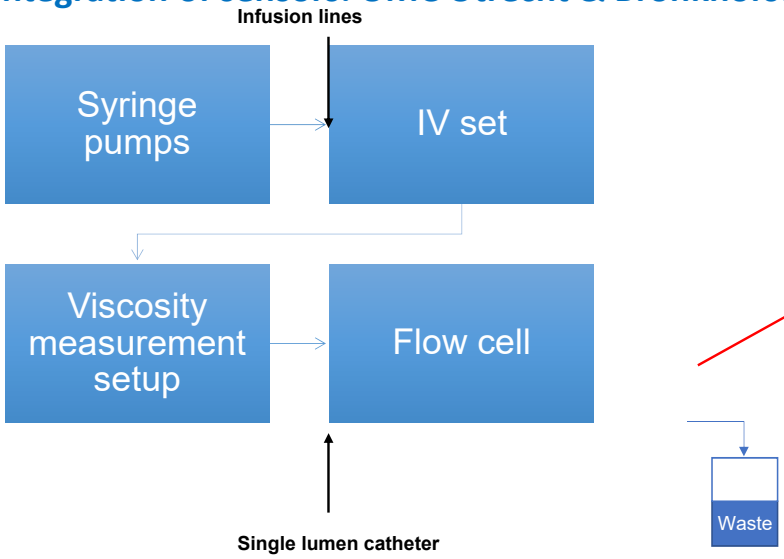
Integration of sensors: UMC Utrecht & Bronkhorst Hightech

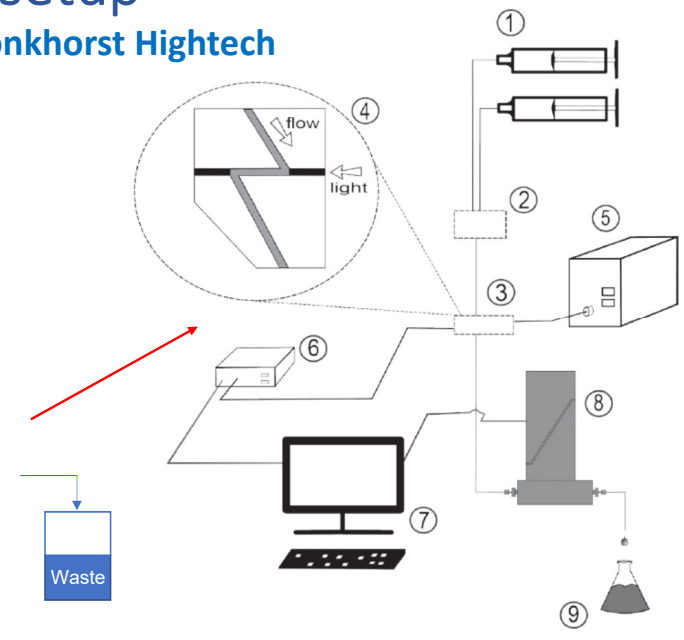




Designing a multi-infusion setup

Integration of sensors: UMC Utrecht & Bronkhorst Hightech





Designing a multi-infusion setup - conclusions

- It is important to speak with clinicians to find out what problems need to be solved
- From the questionnaires and interviews, we got a clear idea what the problems in clinical practice are
- Multi-infusion setups should be divided in the setup under investigation and the measurement setup
- For the setup under investigation clinical relevance is most important
- At the same time the clinical environment has very unstable working conditions (temperature, dosing requirements)
- For the measurement setup the equivalence to clinical situations and stable measurement conditions
- At the same time measurement system components influence the flow
- Though it is complex to satisfy both requirements a clear test matrix was agreed upon and working setups could be designed

The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

Thank you!
Metrology for drug delivery team at our last live meeting
METAS, Switzerland February 2020

The EMPIR initiative is co-funded by the European Union's Horizon 2020 research and innovation programme and the EMPIR Participating States

Thank you UMC Utrecht Researchers involved in infusion


Prof. Dr. A.C.G. Egberts (Toine), former Head of Pharmacy, Dpt of Pharmacy

Dr. P. Lemmers (Petra) MD PhD, Associate professor in Neonatology, perinatal neurology

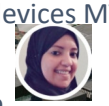
Drs. E. Koomen (Erik) MD, Anesthesiologist and pediatric intensivist, Pediatric Intensive Care

Dr. Ir. A.M.D.E. Timmerman (Annemoon), Medical Physicist, Infusion medical physics
Dpt of Medical Technology and Clinical Physics (MTKF)

Dr. Ir. J.E.N. Jaspers (Joris), Associate professor labour saving devices, MTKF Dpt

Dr. M.K. Konings (Maurits), Senior Research Physicist, inventor of medical devices MTKF Dpt

S. Mejri PhD (Sabrine), Senior Clinical Physics Researcher



Ir. B. Riphagen (Brechtje), Entrepreneur, owner of Innofuse

Dr. Ir. R.A. Snijder (Roland), Medical Physics Resident

Ir. P.P.A. Klaver (Paul), Medical Physicist, clinical research

Dr.ir. A.I. Rem (Alex), Medical Physicist, e-learning

Dr. A.R. Onur (Sander), Medical Physicist, e-learning

Ir. R.J.F. Gevers (Robin, Medical Physicist Resident

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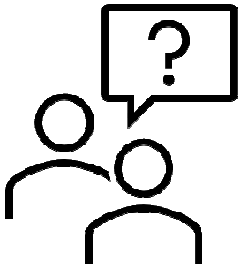

Questions?

Join this afternoon's discussion

Or check https://drugmetrology.com/

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