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Clinical relevance of metrology for drug delivery

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Drugmetrology.com

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Relevance of metrology for drug delivery: a clinical case

Preterm neonate: (gestational) age

28 weeks

Patient mean blood pressure drops to 25 mmHg, goal: 28 mmHg

Low blood pressure and frequent pressure changes can lead to brain damage

Need to increase the blood pressure

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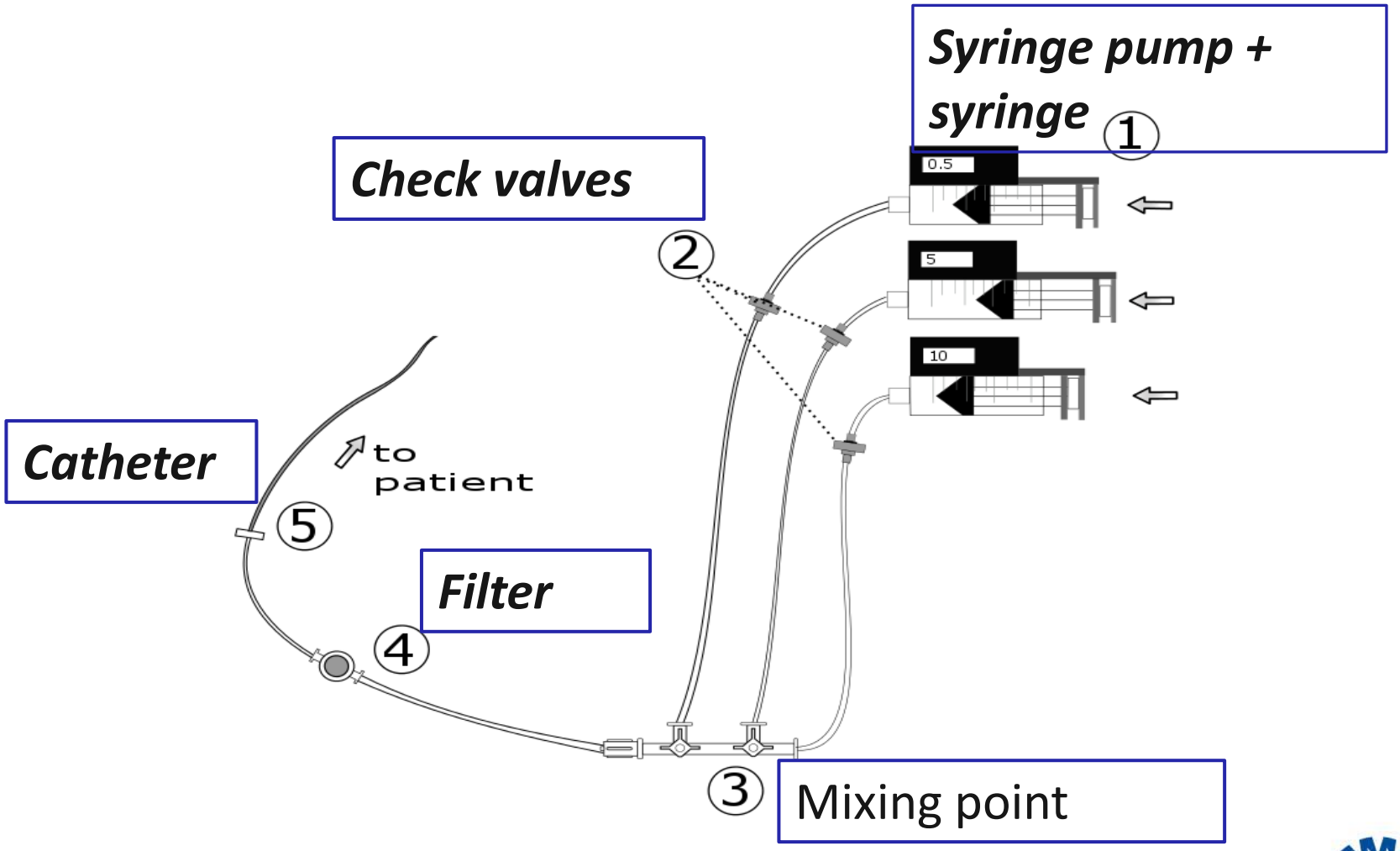
Patient (age 28 weeks) has mean blood pressure: 25 mmHg. Goal = 28 mmHg

- Start treatment: 0.5 ml/h Dopamine infusion
- After 30 minutes, no visible effect: increase Dopamine infusion to 0.7 ml/h
- 30 minutes later: mean blood pressure is 50 mmHg Too high!
- Set Dopamine infusion lower again
- Remains high

This is exactly what we want to prevent!

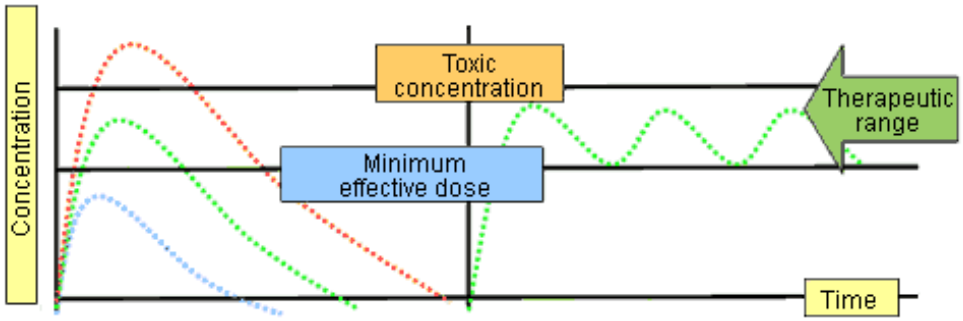
Typical multi-infusion setup



Why is multi-infusion difficult?

Hard to administer right amount of drug

- Condition of the patient:
  - Restricted fluid intake (especially NICU)
- Some drugs are:
  - Fast acting
  - Potent (strong)
- Some drugs have a small therapeutic range:
  - Too low or too high dosage is dangerous



More: session 3, Precise and low variability drug dosing, prof dr. Toine Egberts

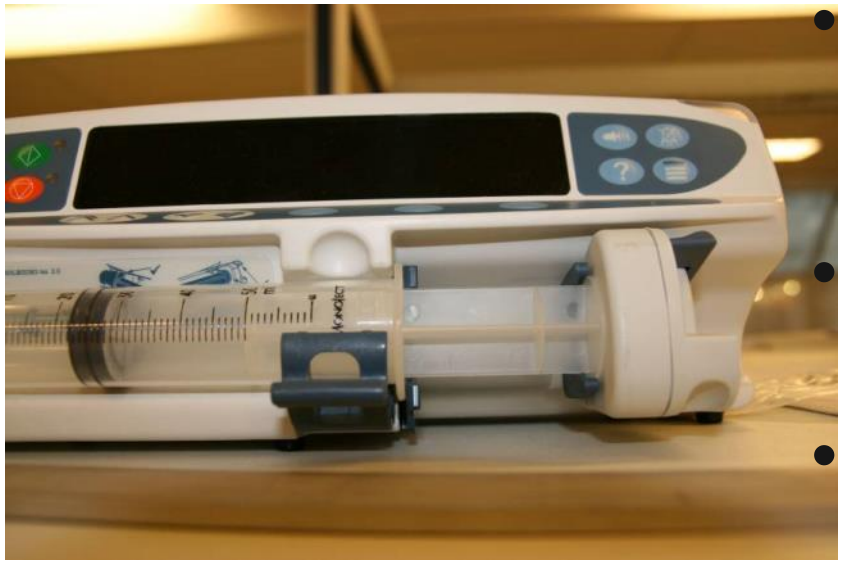
Causes of dosing errors

- Accuracy of pumps only in stabilized situations

- During changes in flow rate two effects play a role:
  - ❖ **Compliance effect**
  - ❖ **Dead volume effect**

- They cause:
  - ➢ Delay in correct drug administration
  - ➢ Temporary overdosing or underdosing

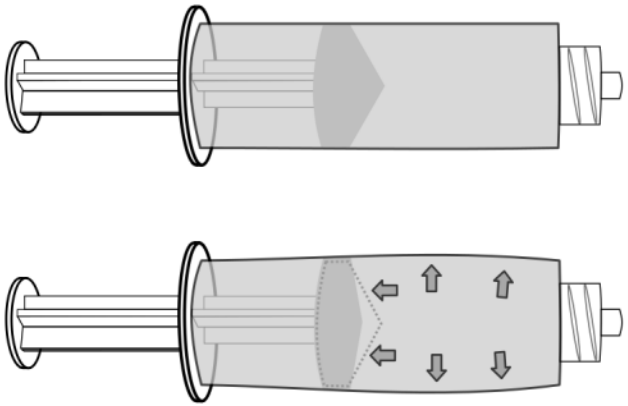
Control mechanism syringe pump infusion



- Driving mechanism:
  - Displacement of plunger by step motor
- Control mechanism
  - Change in step motor velocity
- Setpoint parameter
  - Flow rate

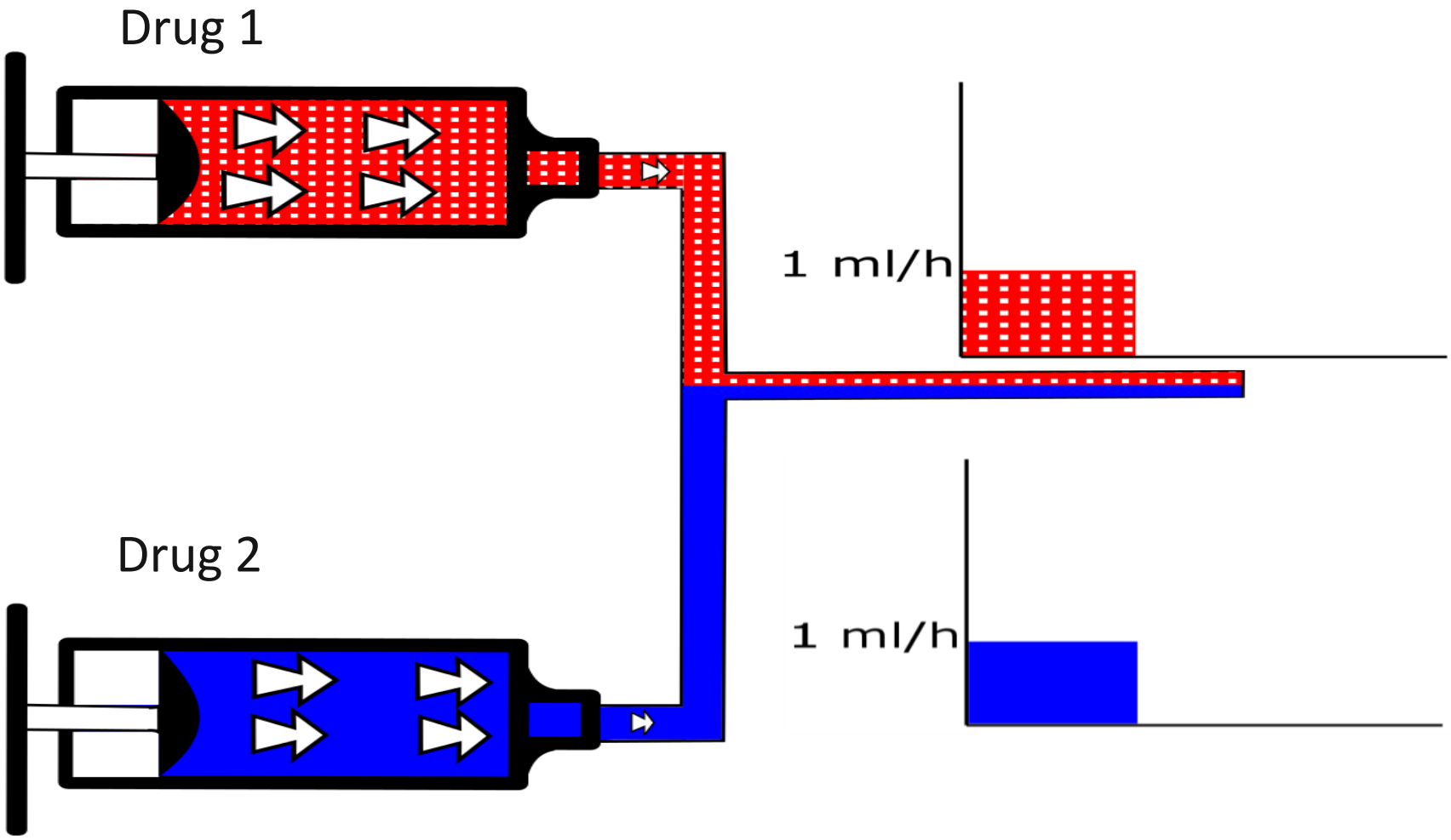
- Non plunger displacement induced flowrate changes are not noticed by the system
- ⟹ poor measurability
- ⟹ poor controllability

System Mechanical Compliance effect

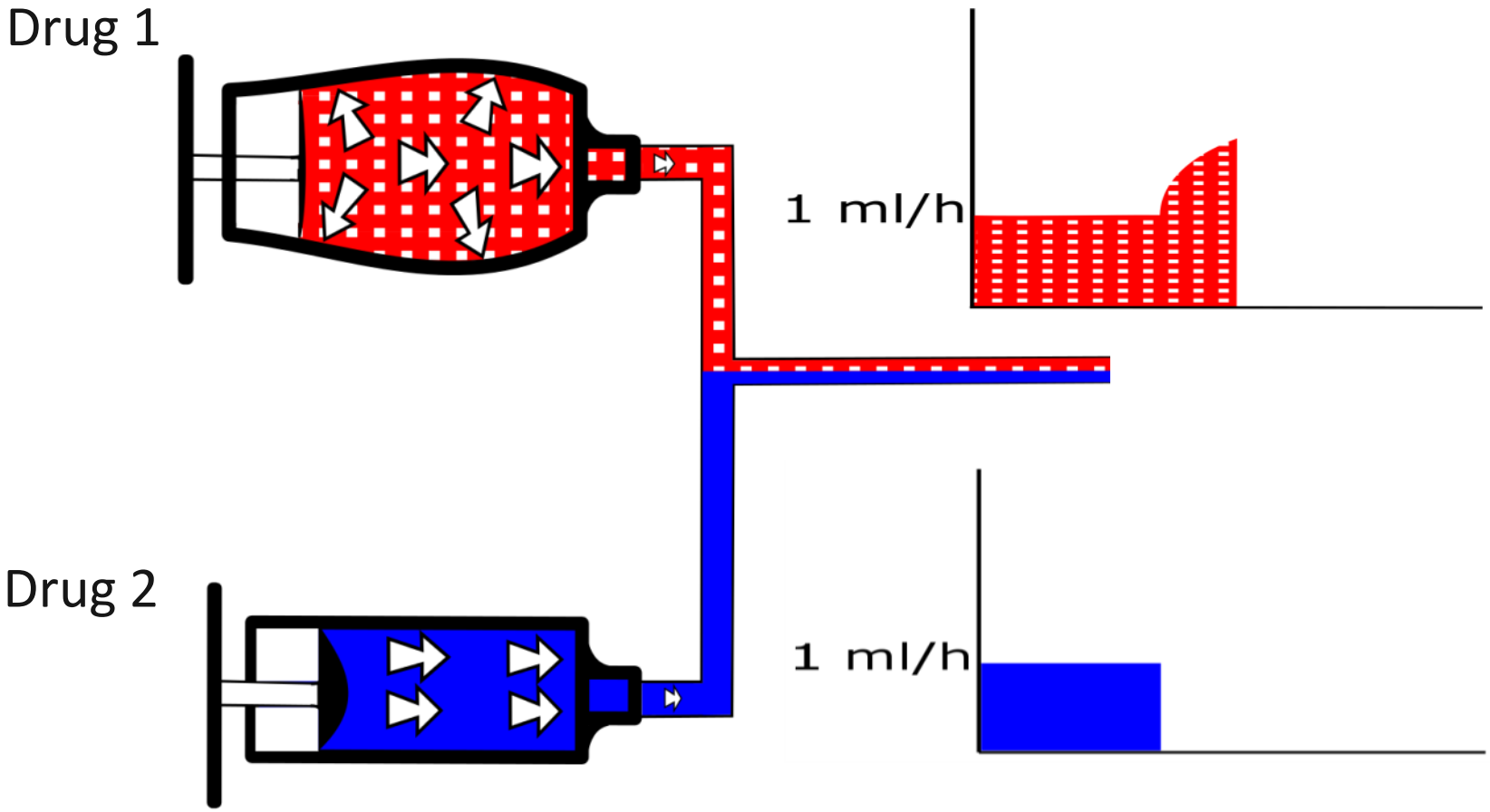


- Compliance: deformation of components at pressure changes
- On pressure increase fluid is stored inside parts of the system
  - Does not enter the patient
- Clinical situation: 2 syringe pumps. setpoint of 1 pump is increased
  - output of new dose of drug 1 is delayed
  - Temporary dose decrease from drug 2

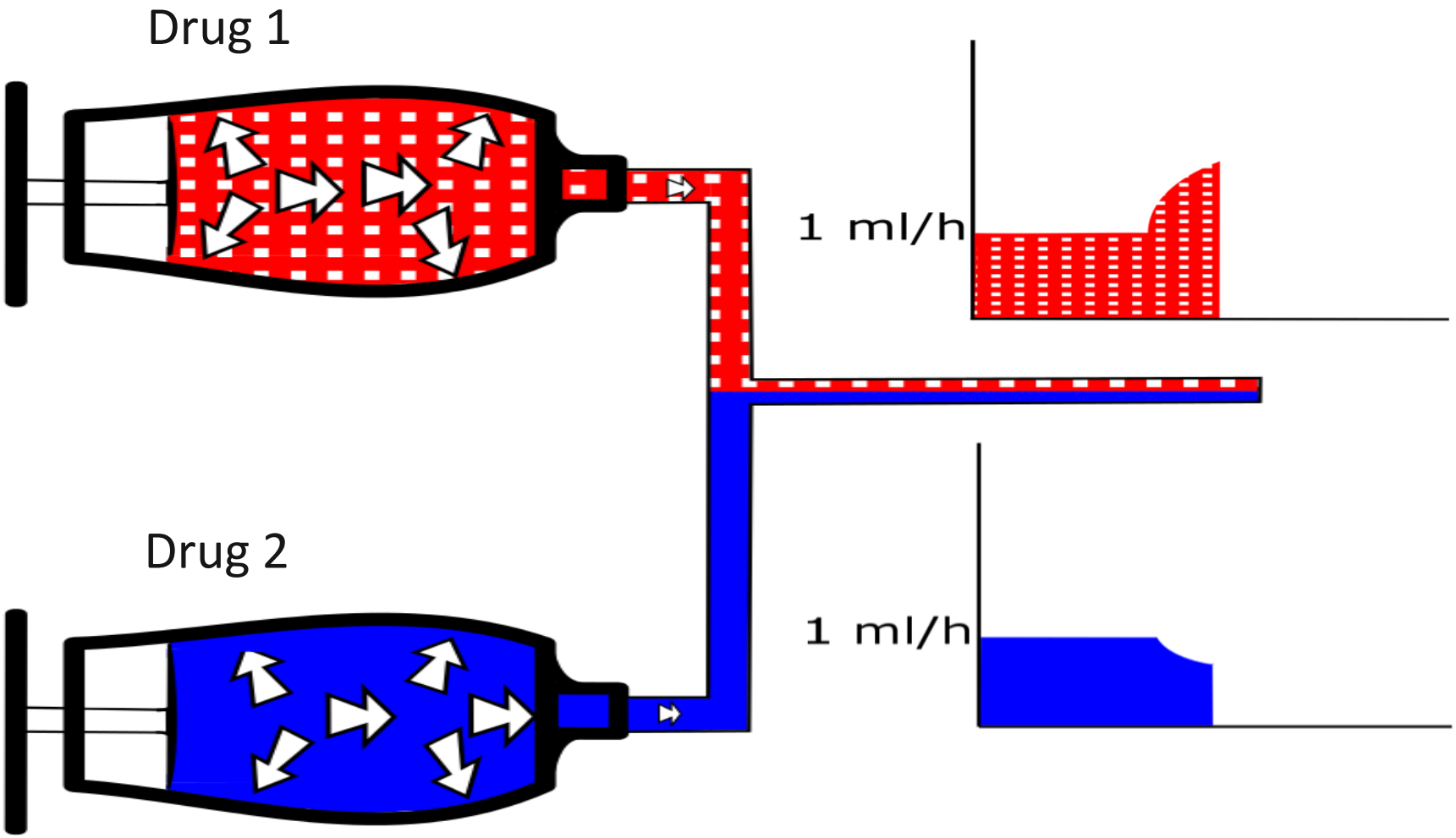
Compliance effect



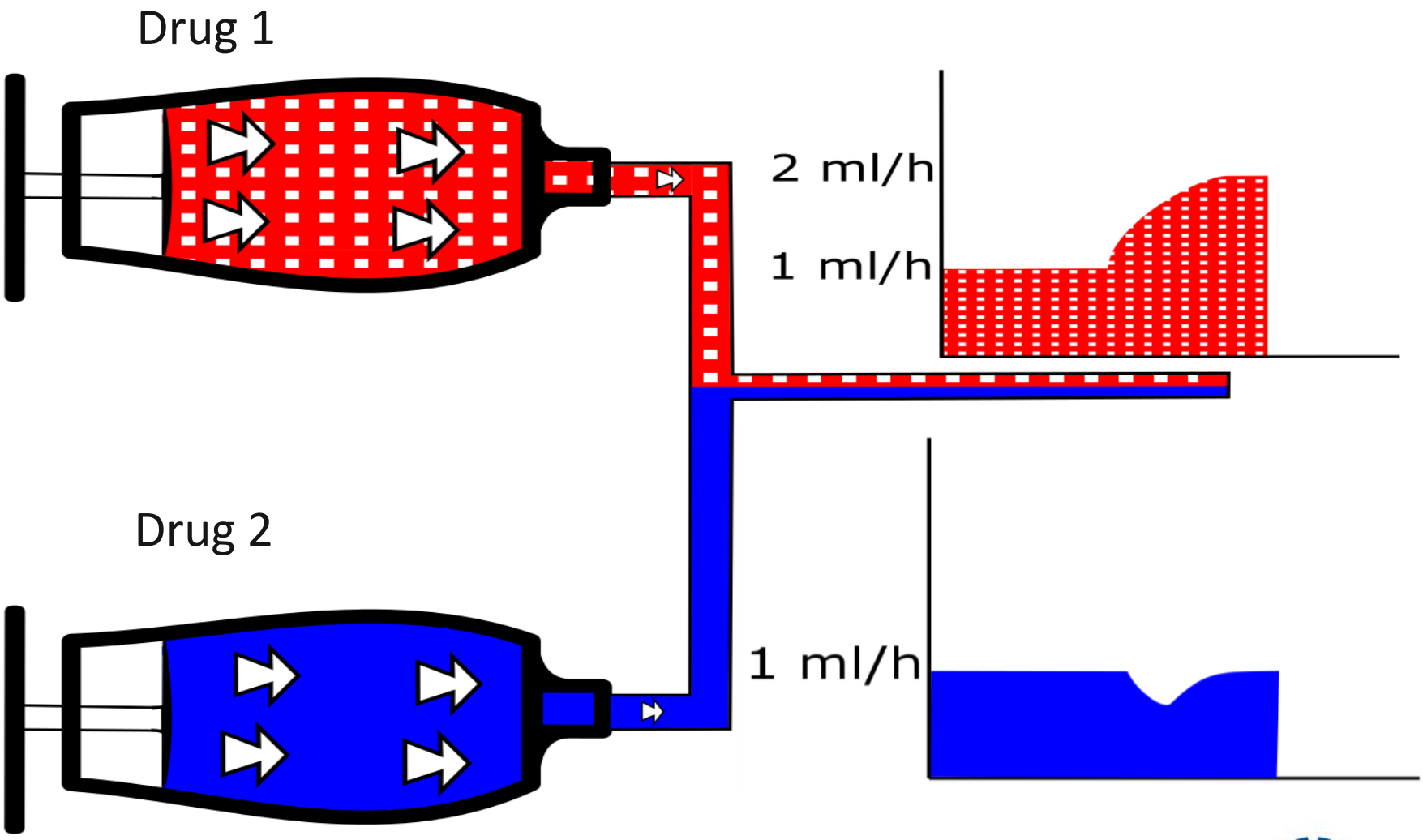
Compliance effect



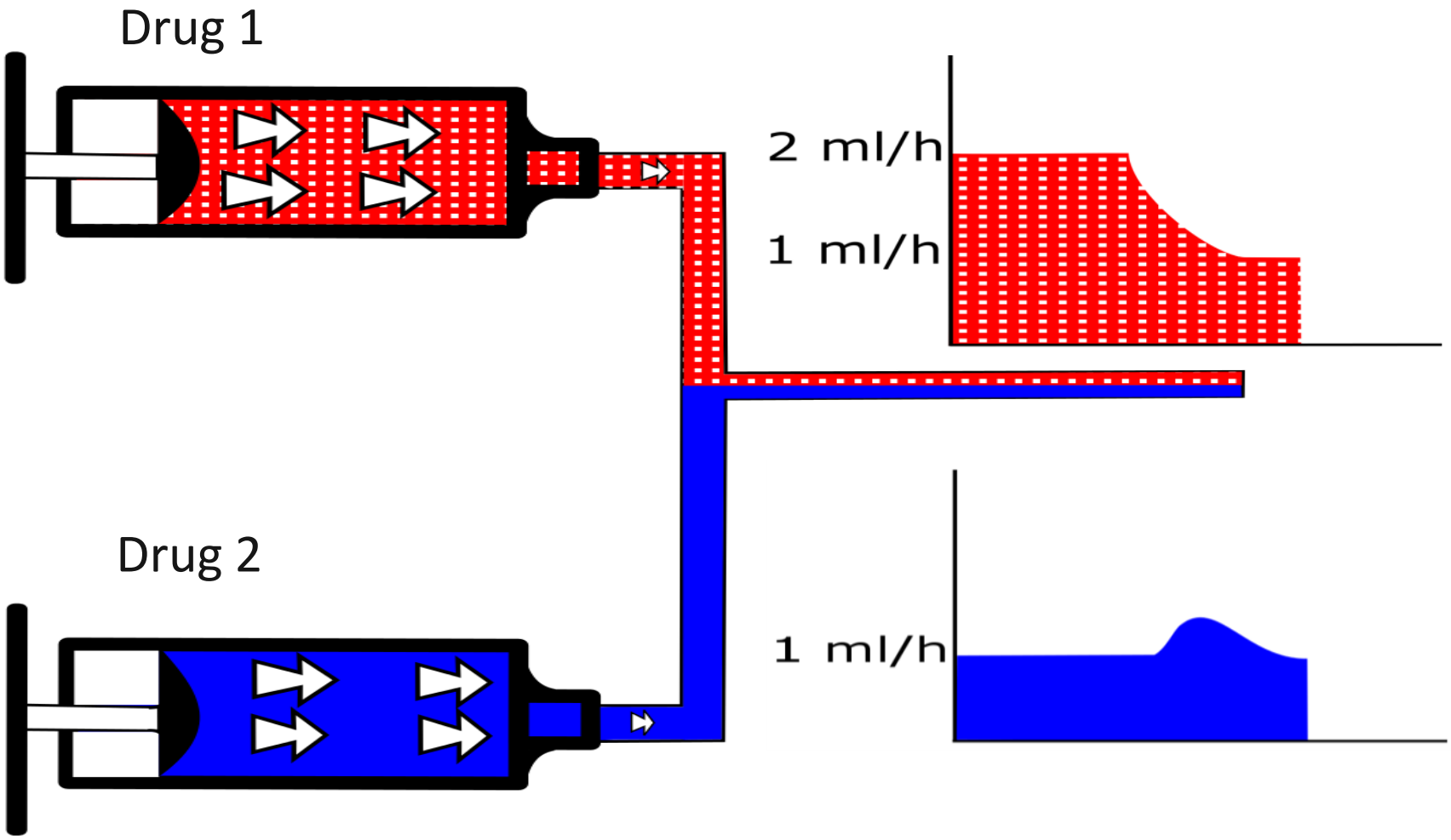
Compliance effect



Compliance effect

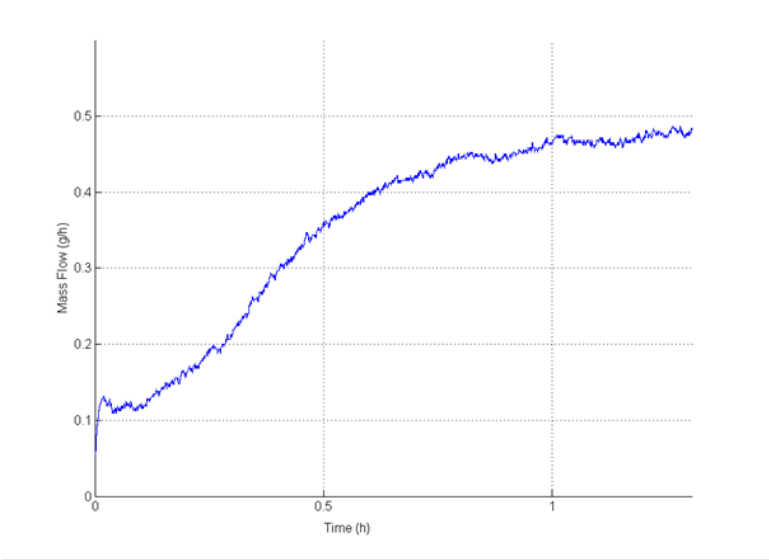


Compliance effect



Clinical relevance compliance effect

- Compliance effects:
  - Components store fluid
  - Delay changes in flow rate
  - Acts in opposite direction to flow rate change
  - If flow rate is low compared to stored volume, the dose effect is large
- Compliance of infusion system components should be measured



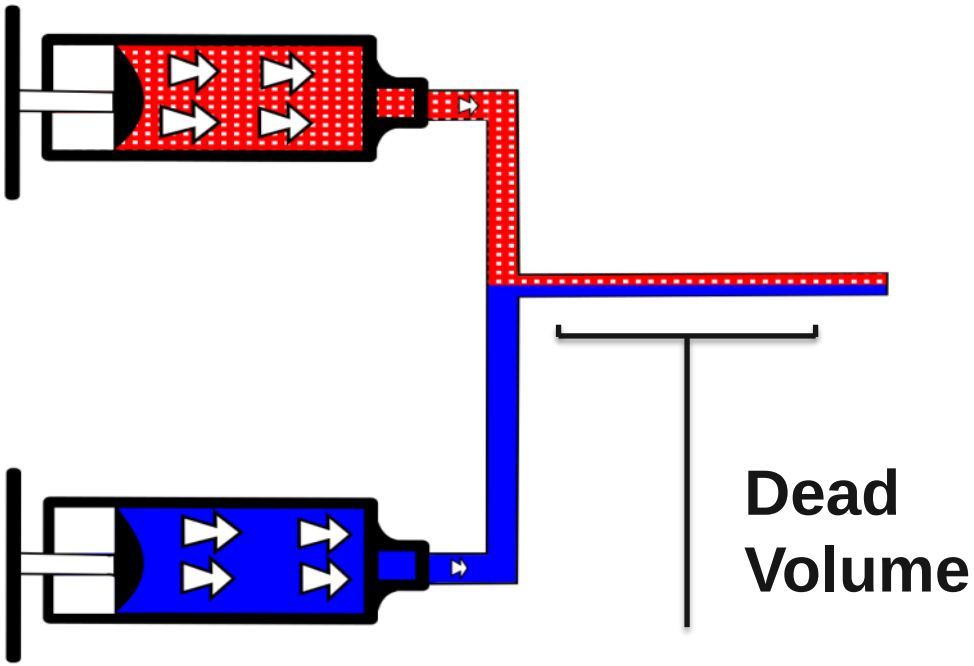
A typical start up curve for an arterial line.

If flow rates < 0,25 ml/h last 10 minutes, blood clotting can occur

More: session 4, Assessment of several drug delivery devices, Elsa Batista, IPQ

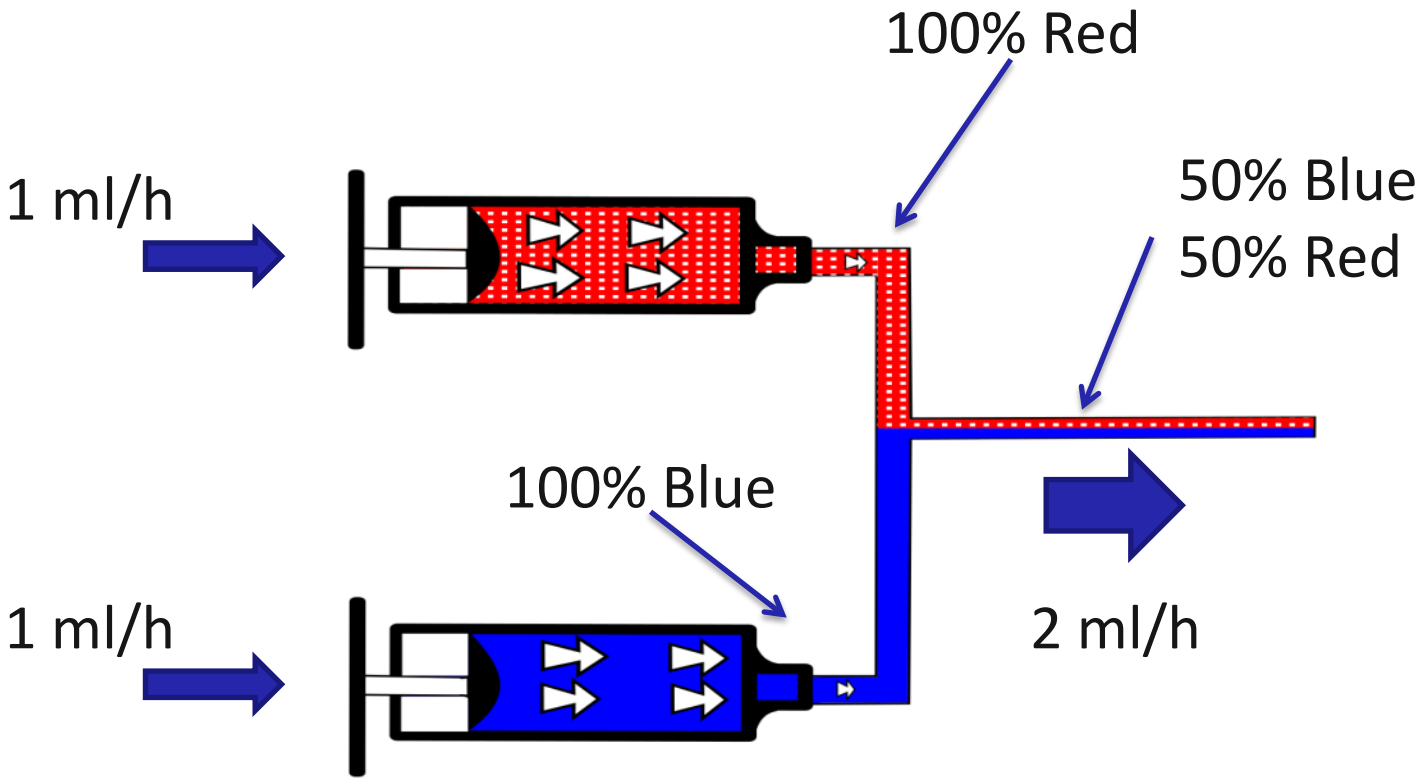
Dead Volume effect

- Dead Volume:
  - Volume of lines etc. **after** the mixing point



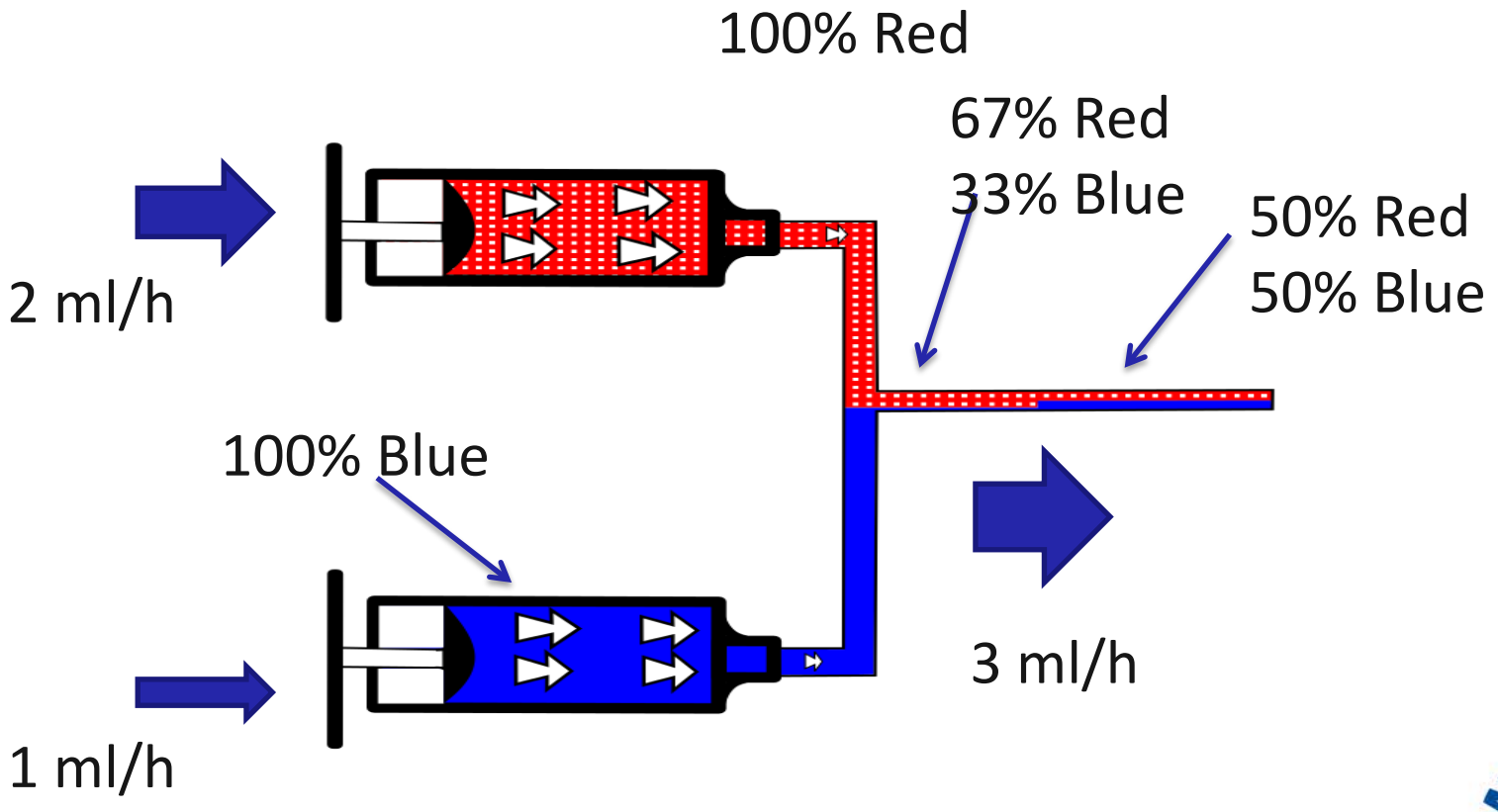
Dead Volume effect

- The contents of Dead Volume are always flushed at the combined flow rate of the pumps:



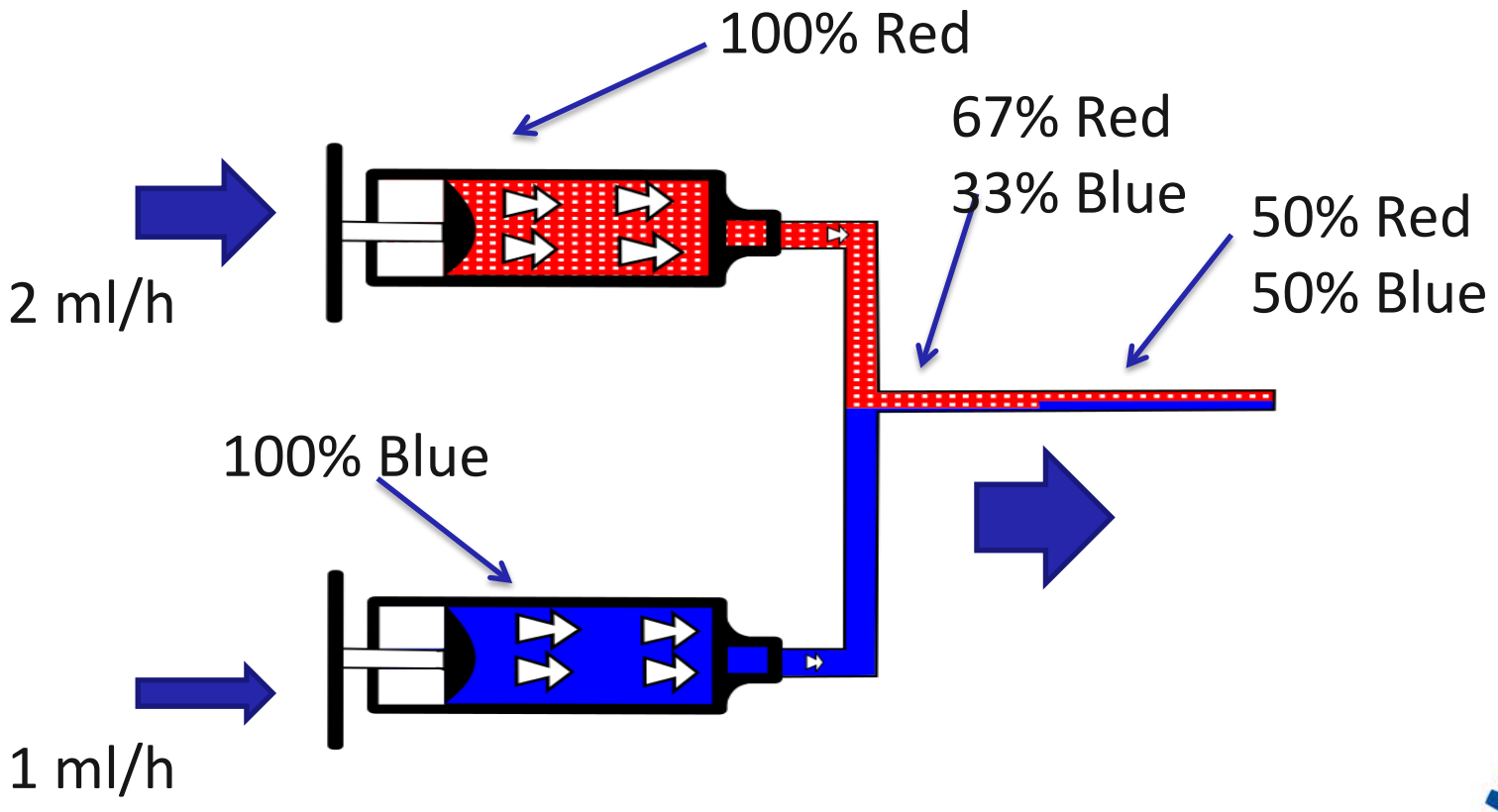
Dead volume effect

- Now we change the flow rate of one pump



Dead Volume effect

- Unintended dosing during Dead Volume flushing
- Intended Flow Rate Change is delayed



Dead volume effect

- Clinical case:
  - Female patient, 62 years of age, no history of disease, had a subarachnoid hemorrhage yesterday is operated for clipping of aneurysm
  - Blood pressure has lowered too far after induction and inserting arterial line and central venous pressure device
  - Noradrenaline therapy is started using a saline carrier flow
  - Onset of blood pressure increase has not started after 15 minutes!
  - Anesthetist increases flow rate
  - After 20 minutes blood pressure increases too much
  - Anesthetist stops noradrenaline therapy
  - Blood pressure keeps increasing: a rebleed occurs

- Dead volume effect:
  - At flow rate change volume after mixing point, having old concentration ratio
  - acts in same direction as the flow rate change
  - Clinically relevant dosing errors occur mostly at high flow rates

Standards and regulations

- Pumps: IEC/EN 60601-2-24
  - Describes “trumpet curve”
- Syringes: ISO 7886-2 TC 84
  - Describes maximum compliance
  - Describes maximum “dead volume”

→ No specific regulations for low flowrate/ specific applications (Compliance might be 3x one hours dose)

→ No protocols describing maximum internal volume

→ No output measurements of entire system (pump+syringe+infusion line and catheter)

Dosing errors: the consequences

- High flowrates, urgent acting (e.g. modifying blood pressure in a SAB clipping of aneurysm procedure:
  - Possible overdosing of Noradrenaline due to misunderstood internal volume, causing rebleeding
- Low flowrates, stabilising neonatal conditions:
  - Possible flowrate variations due to height differences of pumps: variations in cerebral blood pressure, harmful to the brain, bleeding
- Low flowrates, use of volumetric pump:
  - Cyclic variations in dose

Conclusion

- Compliance
  - Delays flow rate change
  - Acts in opposite direction to flow rate change
  - If flow rate is low compared to stored volume, the dose effect is large
  - Clinically relevant dosing errors occur mostly at low flow rates and with fast acting drugs with a small therapeutic bandwidth

- Dead volume effect:
  - At flow rate change volume after mixing point, having old concentration ratio
  - acts in same direction as the flow rate change
  - Clinically relevant dosing errors occur mostly at high flow rates and with fast acting drugs with a small therapeutic bandwidth

- For each flow rate change: combination of Dead Volume and Compliance effects
  - Delay in intended administration change
  - Dosing errors contrary to expectations of user
  - Dosing errors in the **other** pumps as well

More: session 4, Dosing errors in multi-infusion, Roland Snijder, UMC Utrecht

Take home

- System mechanical compliance
  - should be measured, especially for low flow rate applications and for applications using fast acting drugs with a narrow therapeutic bandwidth
  - adaptation of standards for critical application should be seriously considered
- Dead volume
  - effects can cause very serious and even fatal effects, especially in high flow rate critical applications
  - Should be taken into account for establishing infusion system performance

- We still are in desperate need for innovations in infusion devices, mitigating these effects

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Questions

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Disclaimer

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