Quality Relevant Aspects in the Design and Performance of Pharmaceutical Water Systems

Workshop of the Turkish Pharmaceutical Ind.
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Content of Presentation

1. Pharmaceutical Water
2. Water treatment technologies
3. Design aspects Distribution Systems
4. Qualification
5. Summary

1.1 Pharmaceutical water qualities

➔WPU: Purified Water/Aqua purificata

- TOC: < 500 ppb
- Conductivity: < 1,3 µS/cm at >25°C without T-comp.
- Micro-organisms: < 100 cfu/ml

➔WFI: Water for Injection/Aqua ad injectabilia

- TOC: < 500 ppb
- Conductivity: < 1,3 µS/cm at >25°C without T-comp.
- Micro-organisms: < 10 cfu/100 ml
- Endotoxins: < 0,25 EU/ml (LAL-Test)

1.2 New test methods as per USP XXIV

Previously:	Currently:
pH	Deleted, acc. to a note published in July/August 1997 put into force in Mai 1998
BET	kept
Calcium	Conductivity (acc. to USP method <645>
Sulfate	
Chloride	
Ammonia	
CO_2	
Oxidizable substances	TOC
Heavy metal	deleted
Total solids content	deleted
Coliforms	deleted
(Microbial count)	added (see USP chapter <1231>)

2. Water treatment technologies

Water treatment system consist generally of the following components:

1. Water pre-treatment (to achieve chlorine free, softened water)
2. Water purification (to achieve PUW, purified water)
3. Water distillation (to achieve WFI, water for injection)

2.1 Water pre-treatment

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Der Schritt voraus ...

Anlagenschema: **Wasservorbehandlung**
Plant-Scheme: Water pre-treatment

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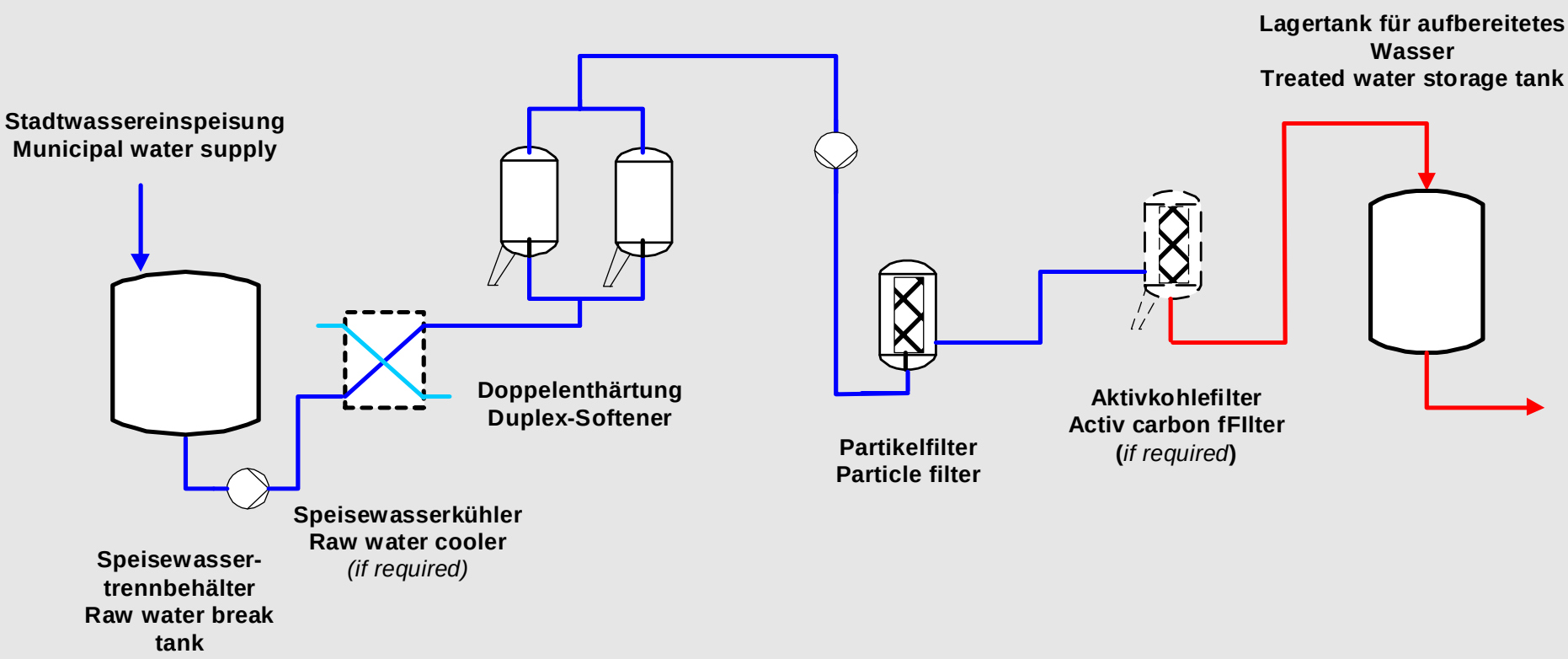

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2.2 Water purification

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Anlagenschema: **Wasserreinigung**
Plant-Scheme: Water purification

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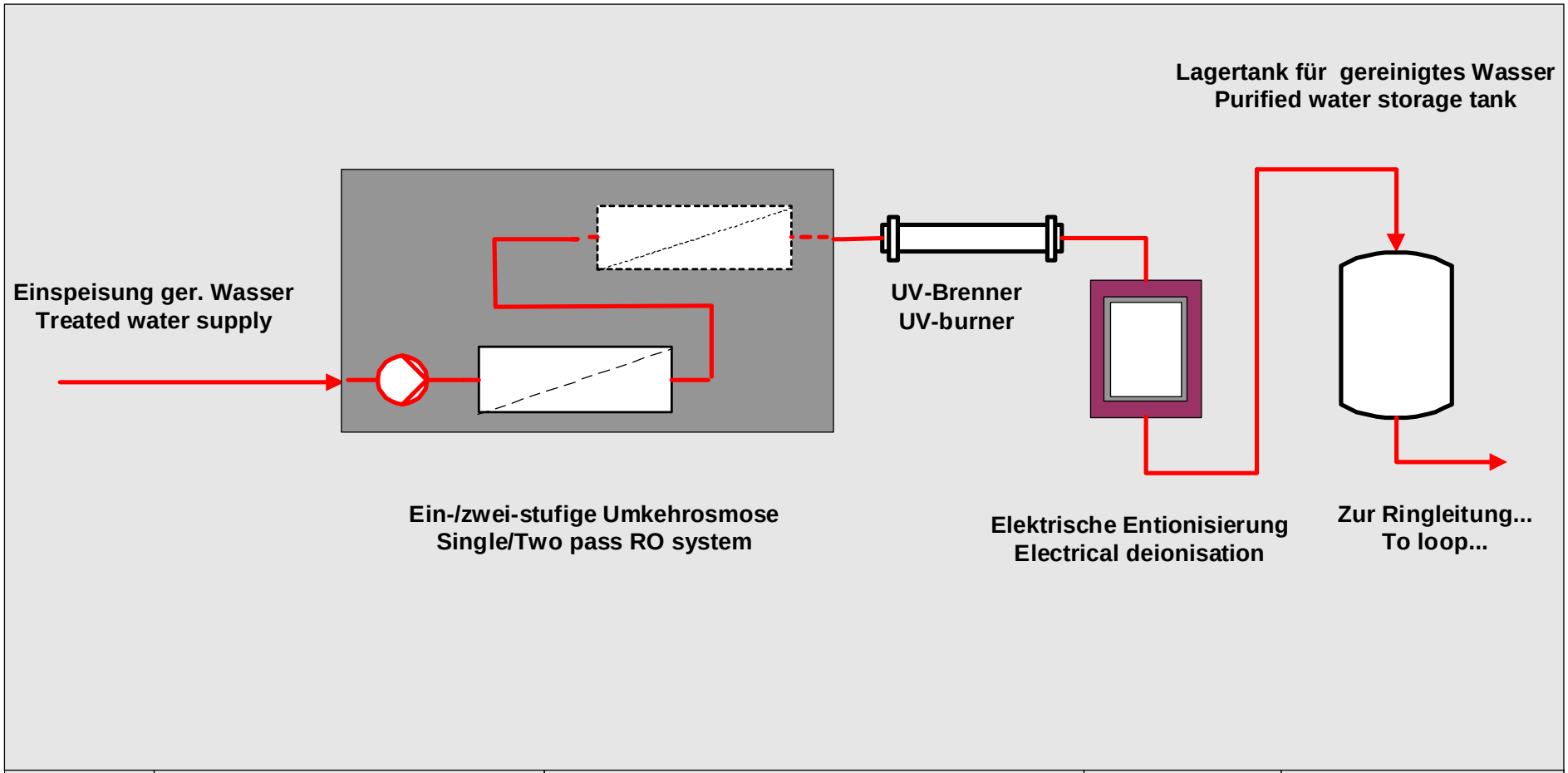

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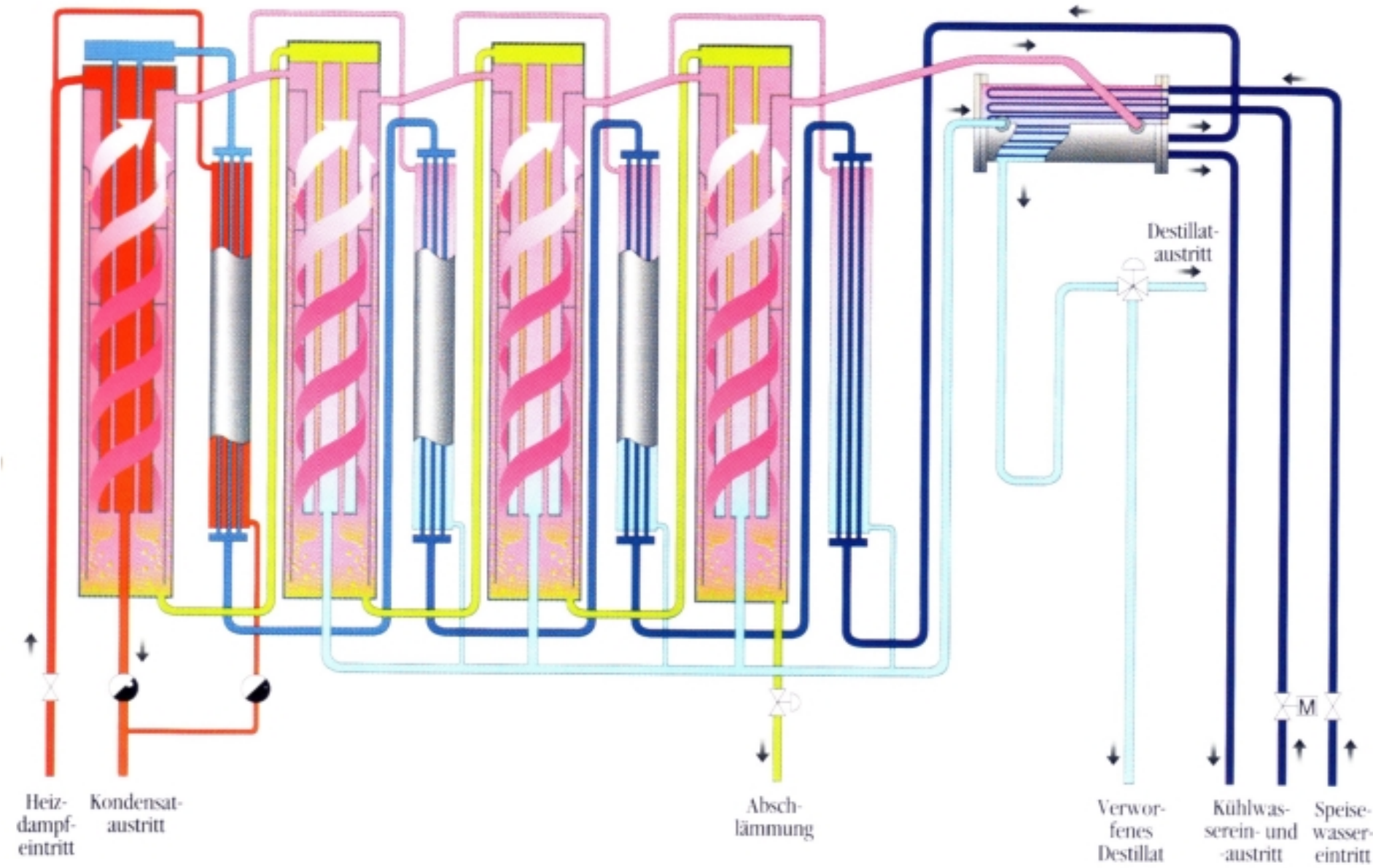
2.2 Water purification systems

2.3 Water distillation



2.3 Water distillation technologies

Water distillation systems

3. Design aspects Distribution Systems

In general, a pharmaceutical water distribution system consists of the following components:

- Storage tank
- Distribution system (“Loop”):
  - Circulation pump
  - Valves, heat exchangers
  - Piping with use-points
  - Quality control instruments
- Control and monitoring systems

3. PUW - Distribution Systems

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Der Schritt voraus…

Anlagenschema: **Ringleitung für gereinigtes Wasser**
Plant-Scheme: Loop for purified water

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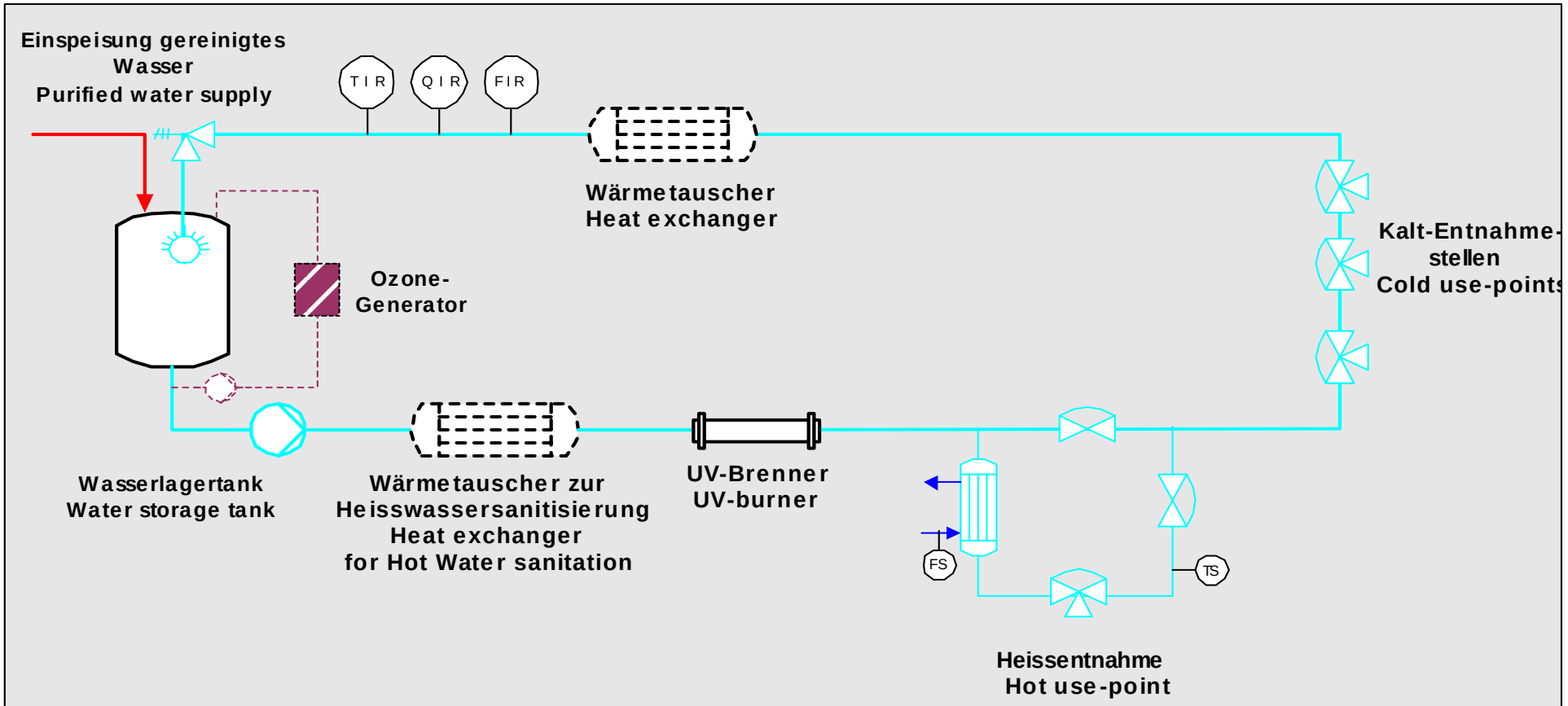

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3. WFI - Distribution Systems

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Anlagenschema: **Ringleitung für distilliertes Wasser (WFI)**
Plant-Scheme: Loop for distilled water (WFI)

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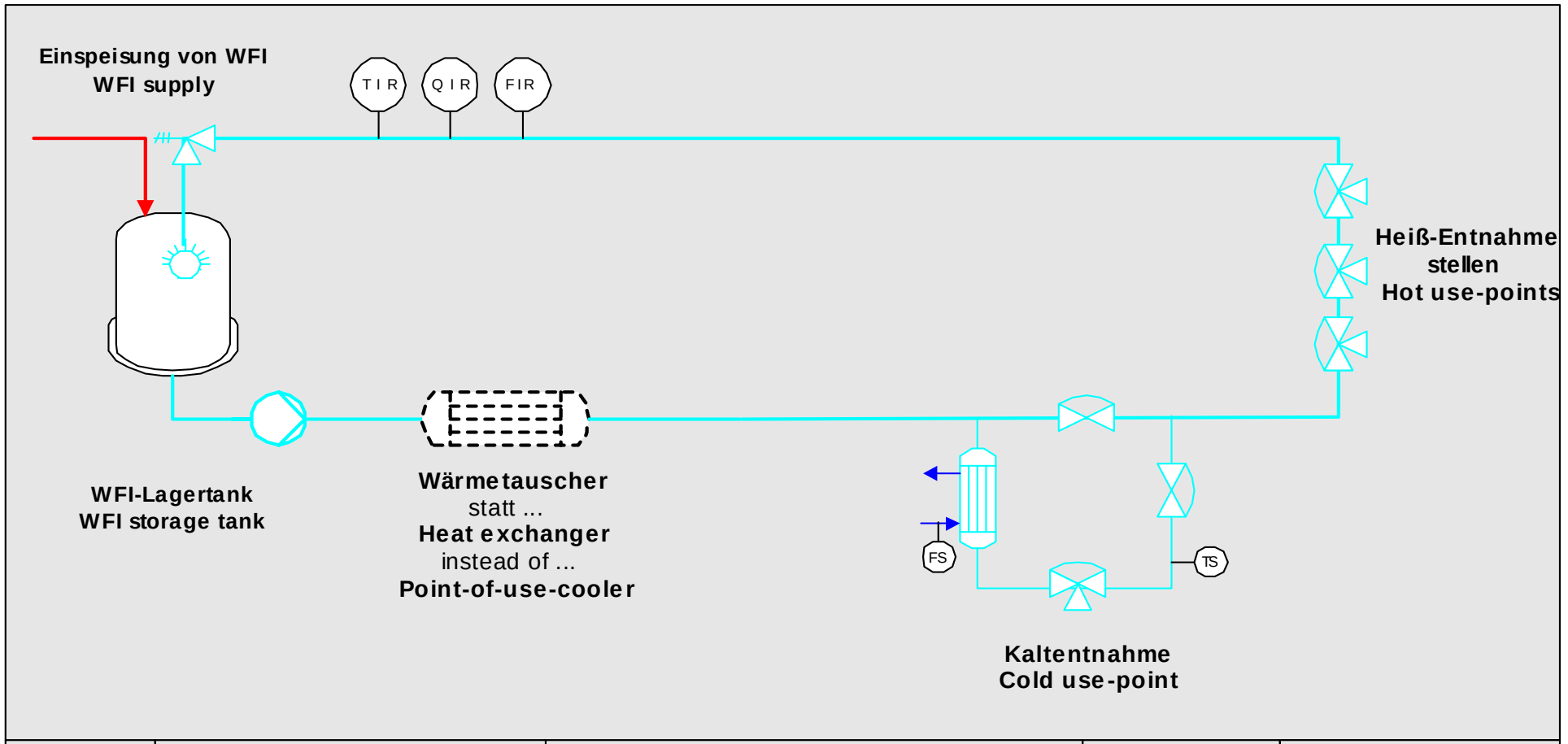

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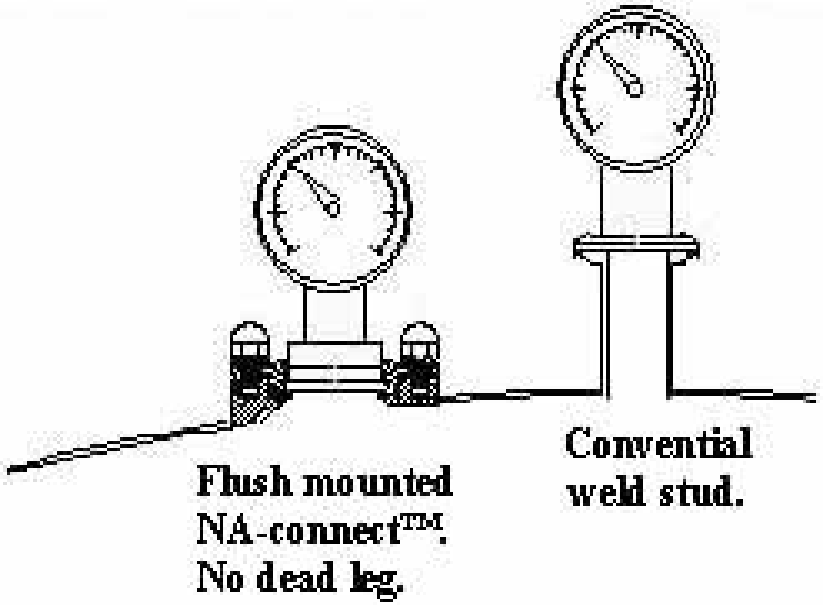
3. Design aspects Distribution Systems

Generally following rules should be observed

- Fully drainable
- Zero dead legs (*as far as technically possible*)
- All connections, sealings etc. free of unnecessary gaps, corners etc.
- Homogene heat up and cool down of the system to prevent thermal shocks
- Gasket material temperature resistant up to 130°C and FDA certified
- Pipe connections of sterile design
- Corrosion safe design
- System should be re-passivated after installation
- Method of microbial control (e.g. UV-burner)

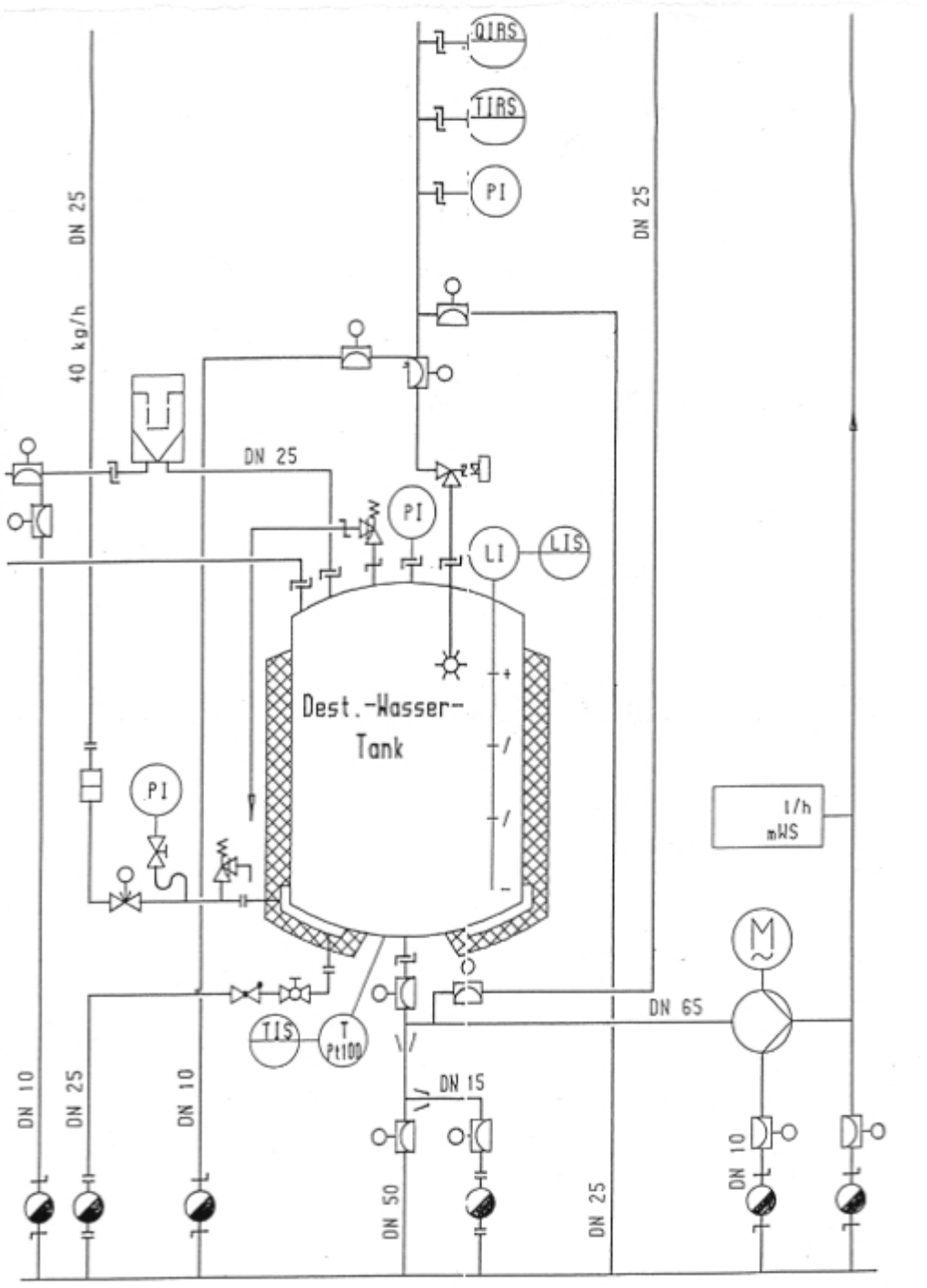
3.1 Storage tanks

- **Mechanical grinding to R_a < 0,4 µm, preferably electro polished**
- **Sterilisable construction:**
  - Pressure and vacuum resistant construction (+3/-1 bar)
  - All accessories installed on shortest possible sockets and of sanitary design, e.g. non-fragmenting rupture discs with safety valve
  - Vessel aeration via sterile vent filter 0,2 µm. In case of hot water storage tanks, steam-heated filter housings should be considered



3.1 Storage tanks

- **Heating via double jacket/bottom, no heating elements inside the vessel**
- **Spray ball at the loop-return inlet in adequate positions for continuous rinsing of the inner vessel cover**
- **Manhole for maintenance**



3.2 Loop Pump

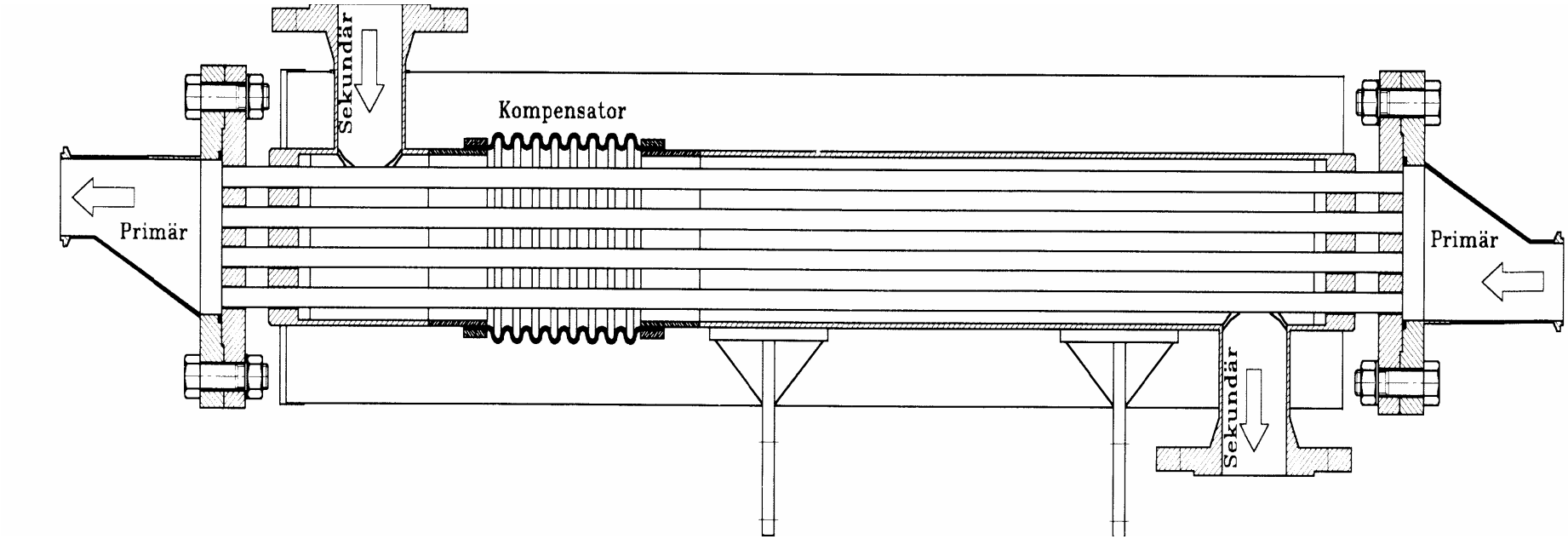
- Suitable sized pump to assure turbulent flow in all pipelines (min. 3 m/s in the loop pre-run). For accurate sizing, following data should be available:
  - Location of loop (one floor, several floors etc.)
  - Number and required flow rate of use points
  - Probability of take-off at the same time
  - Peak consumptions
- Backup-system in case of pump breakdown

3.2 Loop Pump

- Preferably two pumps (adjustable flow rate via frequency converter) running at 50% service. In case of malfunction of one pump, the other takes the service at 100% for a limited time.
- Suitable valve combination to allow a change of one pump including flushing and sterilisation after change, while the loop is still in operation
- Pump housing must have an outlet at the lowest point to allow full drainage

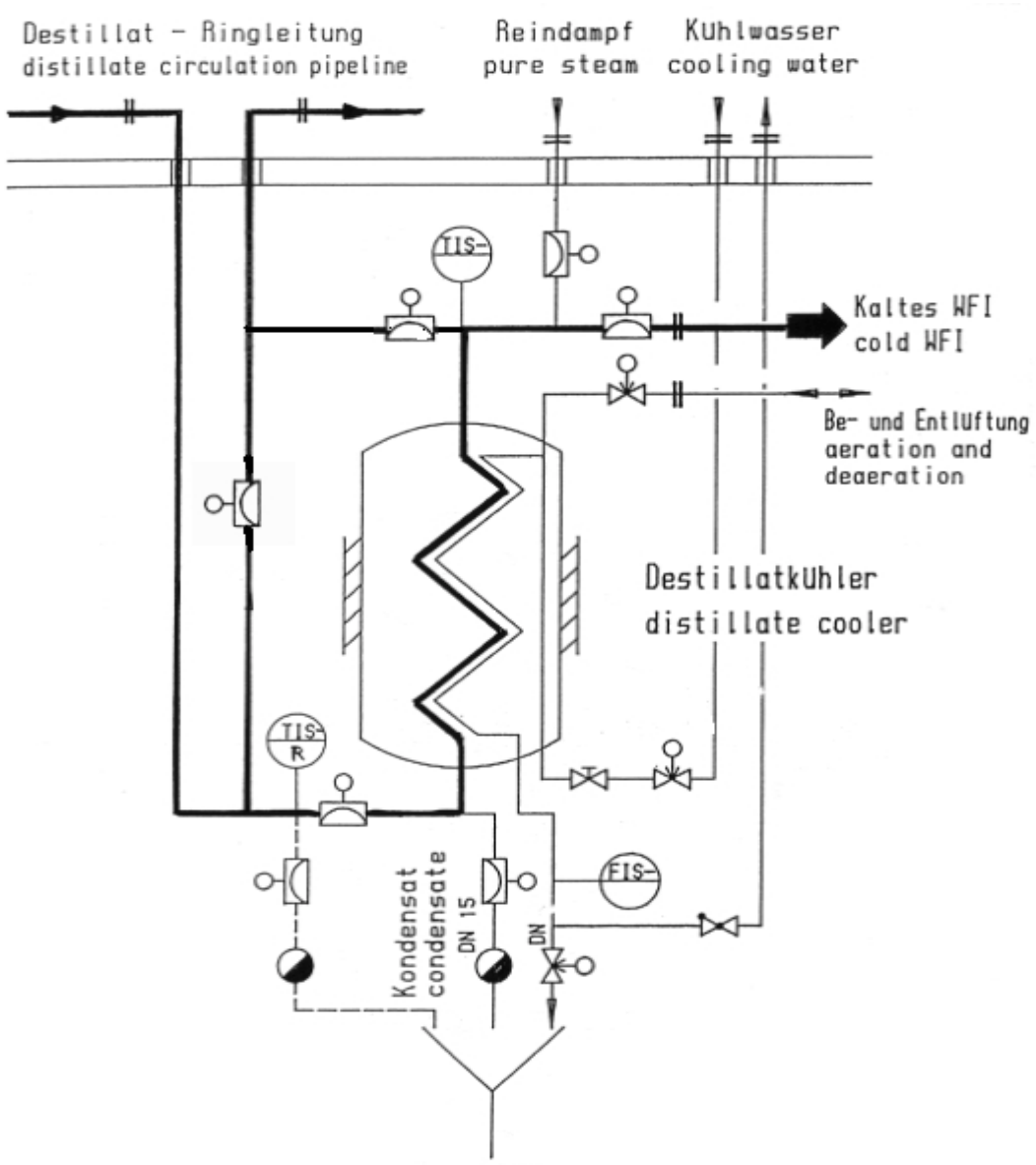
3.3 Heat exchangers

“Cold” loops are usually designed for a hot water sanitation. Therefore heat exchangers in continuous contact with the high quality water are part of the loop and should therefore be of special sterile design (called either double tube sheet or shell&tube)



3.3 Heat exchangers

On “Hot” loops is often required to draw of cold water at the point-of-use. Also here a dead-leg-free design is required



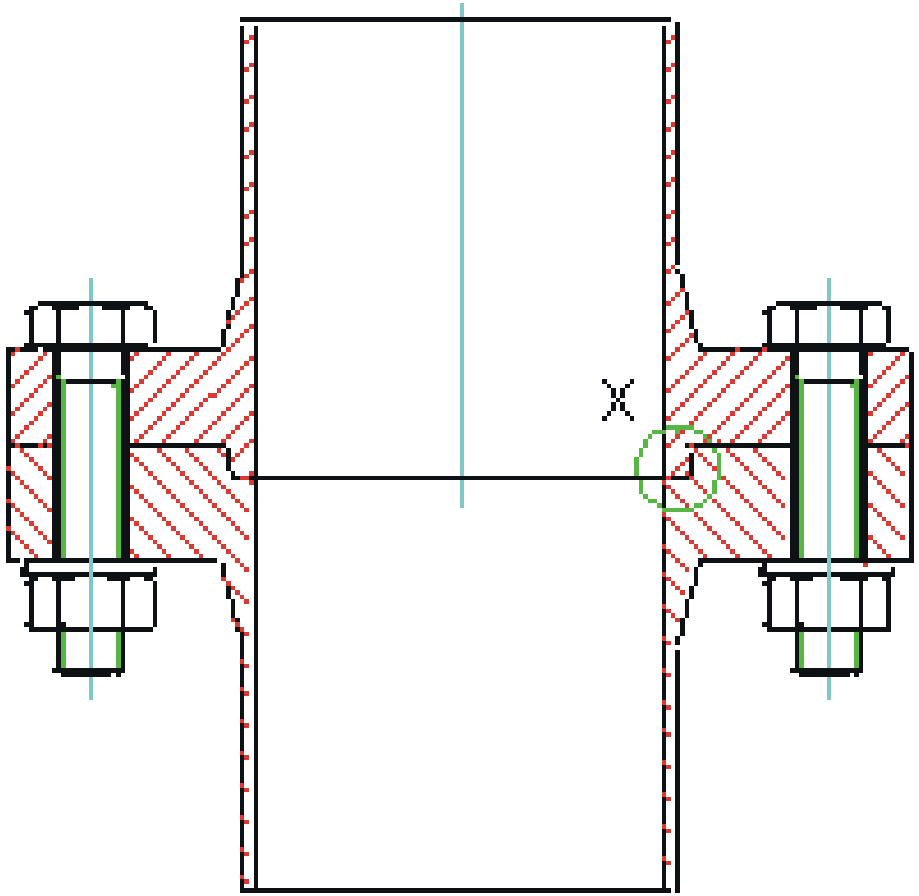
3.4 Pipes and Fittings

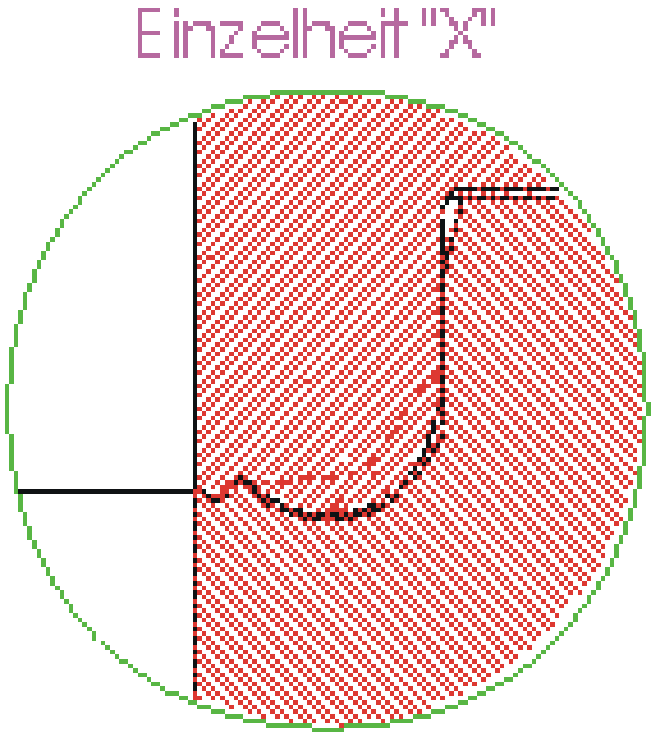
- Wherever reasonable/possible, the ring-main (“loop”) should be welded, preferably by orbital (automatic) welding
- Pipes in technical area’s should be insulated to maintain temperatures in the loop. Insulation must be chlorine free

3.4 Pipes and Fittings

- If a connection must be detachable, the sealing must be without any gap, even when undergoing dynamic pipe stress. Gap-free connections are:
  - Axial locking into position by metal fixing (***NOT available for standard (US) Tri-clamp !***)
  - Dead leg-free sealing installation
  - Centric groove

3.4 Pipes and Fittings





3.5 Construction material

For all parts in contact with product/water only the following material should be used:

- 1.4404 corresponds to AISI 316L
- 1.4435 corresponds to AISI 316L

Should the ΔFe content be of concern, only special melts of 1.4435 can be used.

Both materials can also be perfectly electro-polished.

Alternatively heat resistant PVDF can be used as piping material, but should be well supported to prevent sloops (as stated in the FDA-"*Guide to inspections of high purity water systems*").

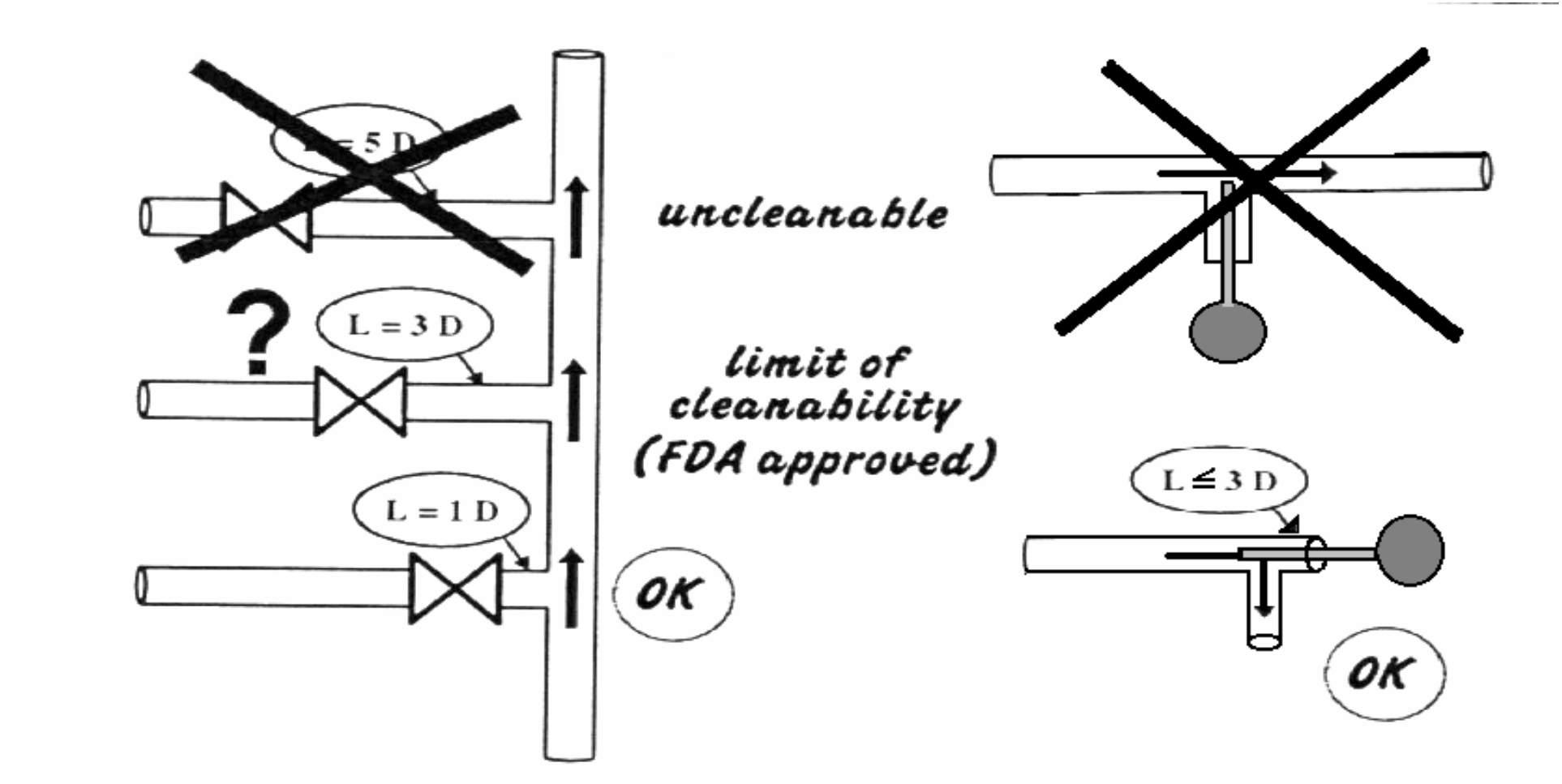
3.6 Material Surface Finish

- In praxis a (very expensive) high-mirror polished surface finish is very often considered more important than a dead-leg-free design.
- Microbiological studies of Hoffmann for CIP-systems state, that the level of the cleaning efficiency (micro organisms removal) is ***not very much*** influenced from the surface quality, even below $R_a < 1$ µm !!

So it may be concluded that an overall inner surface finish for the entire water system, that meets the DIN 11850 (Guideline for Food and Beverage Pipelines) with a $R_a < 0{,}8$ µm (max. 1,6 µm at the longitudinal weld seam of pipes) is indeed suitable !!

3.7 Dead-leg free design

- Avoidance of dead legs in pipe-installations.



3.7 Dead-leg free design

- Use of T-valves at use-points (here GEMÜ:

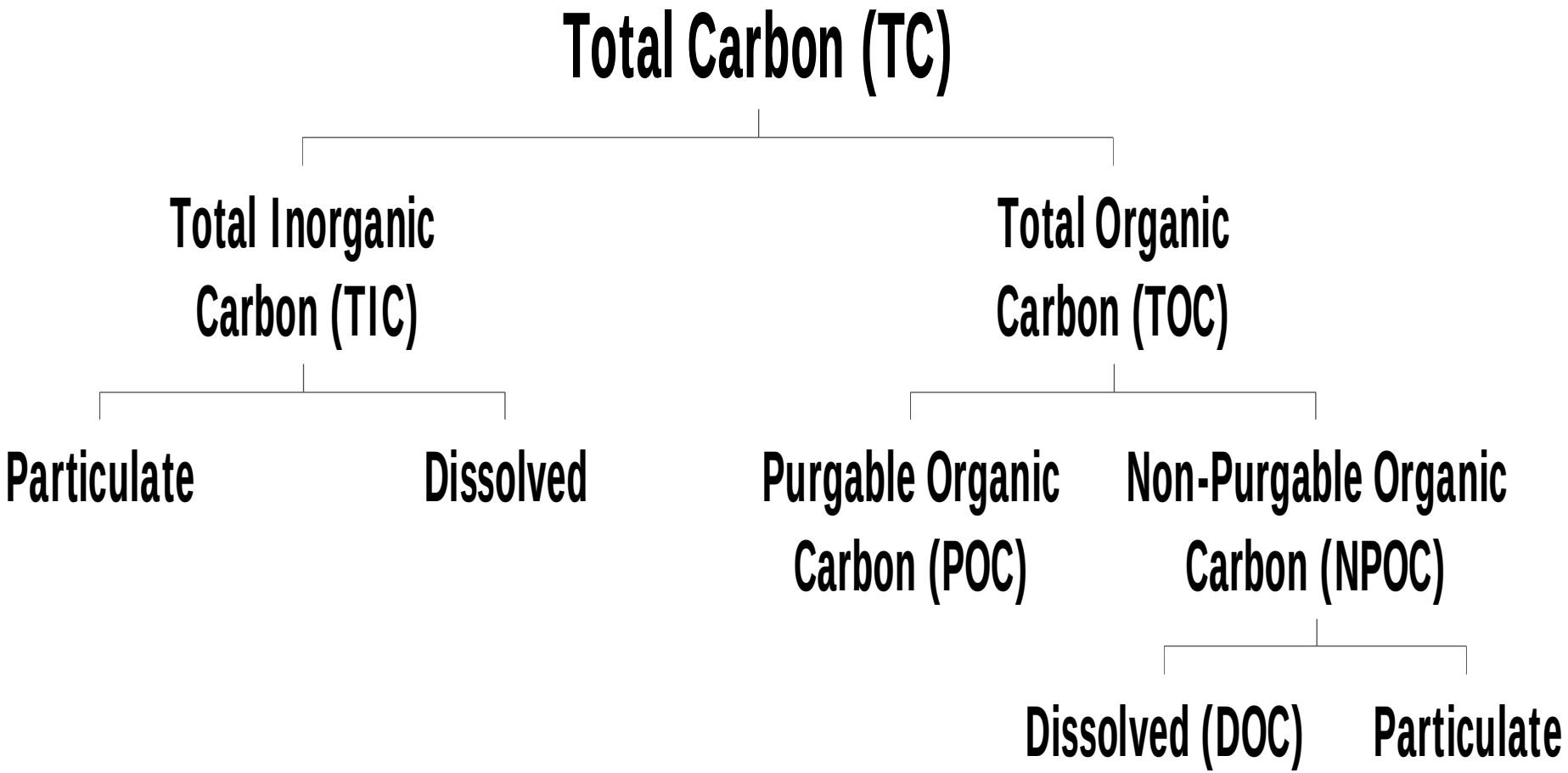
3.8 Instrumentation for quality monitoring

- Temperature control in the storage tank for maintaining a constant/preset water temperature in the loop
- Temperature control and regulation for hot-water sanitation of “cold” loop’s
- Flow control loops for the modulation of the pump flow rate during service- and idle-times and to guarantee a min. flow rate of 0,75 – 1 m/s in the loop return.
- Monitoring of UV-burner intensity. Photometers must be calibrated and must check all lamps.
- Lamps must be replaced at 75% intensity

3.8 Instrumentation for quality monitoring

- Monitoring of temperature in the return-run of the loop
- Metering instrument for the continuous quality control, suitable to decide if the water quality is good or bad. This is usually a conductivity meter.
- Optional: TOC monitoring in loop pre-run and return-run

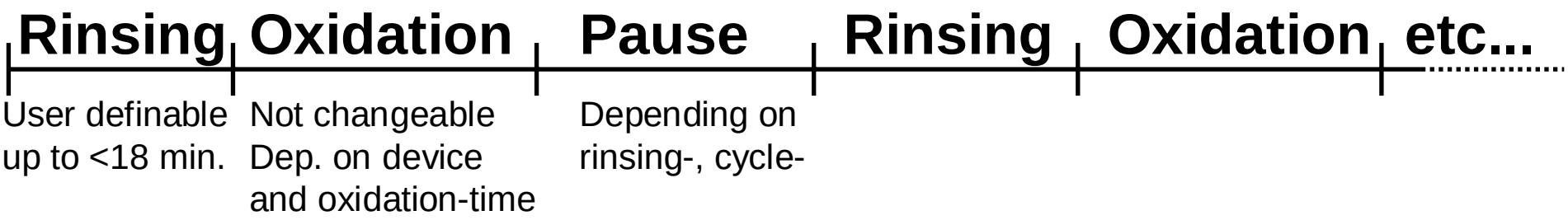
3.9 TOC – Total organic carbon



3.9.1 TOC-content of different water qualities (in mg/l C)

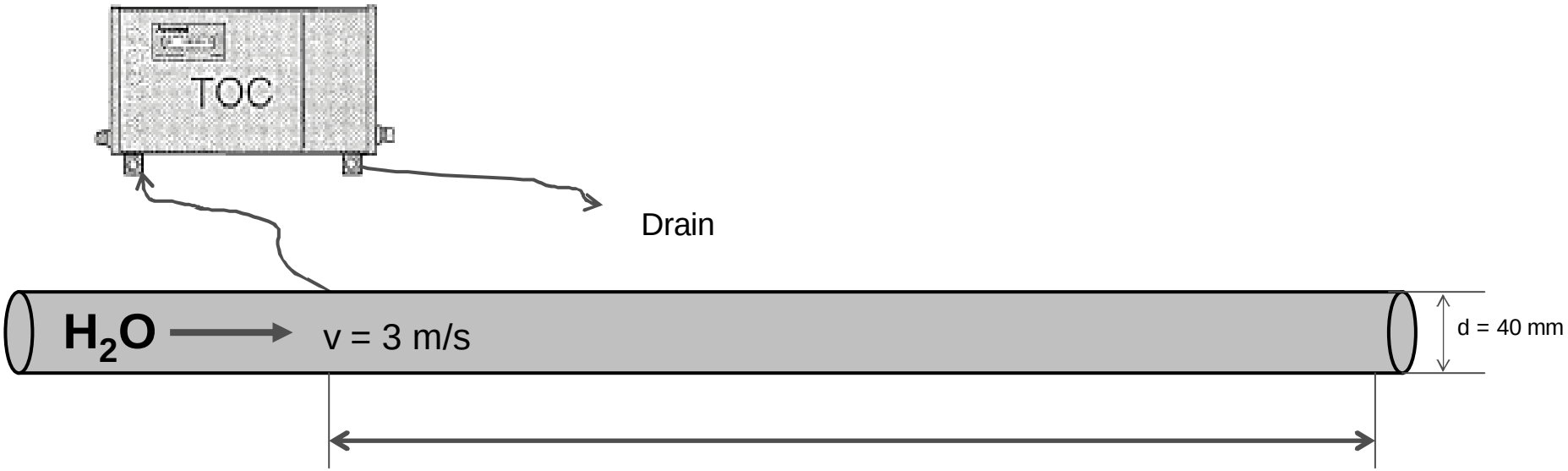
➢ Distilled water	< 0,1
➢ Steam boiler feed water	< 0,1
➢ Deionised water	0,1 - 0,8
➢ Drinking water	0,5 - 2
➢ River water	2 - 10
➢ Industrial drain water	> 10 - 10000

3.9.2 TOC-measuring cycle



On Line ≠ Continuous

3.9.3 TOC-control on water systems



120 sec. = 360 m

or = 460 l

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One step ahead...

3.9.4 Costs

- **Investment:** Depending from the unit and supplier between 30.000,- and 80.000,- € (EURO)
- **Operating cost:** All systems are directly connected to the loop and therefore are potential dead legs. As a workaround they all take continuously water out of the loop.

This is typically between 30 and 600 (!) ml/min or up to 36 l/h (24h/ 7days/ whole year !!)

4. Qualification of water-systems

DQ ,,**Design qualification**“: Establish an exact procedure or a detailed specification after the order, which forms the basis of all further qualification steps.

Required documents:

- Final quotation from supplier
- Official order from buyer

Optional documents:

- P&I-diagram
- Equipment drawings
- Functional description

4. Qualification of water-systems

IQ ,,**Installation qualification**“: Verifies that all quoted items are delivered and installed as specified in the DQ – also sometimes called the “as-built”-check.

Required documents (add. to DQ-documents):

- Final layout drawings
- Final P & I diagram
- Equipment lists
- Process Description
- Certificate of final examination of assembly
- Weld-log, inspection documents and isometrics

4. Qualification of water-systems

OQ ,,**Operational qualification**“: Verifies that the plant performs in compliance with the requirements and functions described in the DQ.

Required documents (add. to DQ/IQ-documents):

- Function test of equipment
- Function test of programme sequences
- Hydrostatic test with print-out of the record

4. Qualification of water-systems

PQ ,,**Process/Product qualification**“: Verifies with treated water that the whole loop works properly. Intensive sampling verifies, that the micro-organisms counts are within their pre-defined limits and stay there over a longer period.

Required[*] sampling as part of the PQ:

- Daily sampling at all use- and sampling-points during start-up phase for 2 - 4 weeks
- Afterwards daily sampling at all use- and sampling-points during performance test phase for 2 - 4 weeks
- Afterwards sampling at min. one use-point, but every use- and sampling-point at least once per week for at least 12 month
- Afterwards continuous sampling acc. SOP

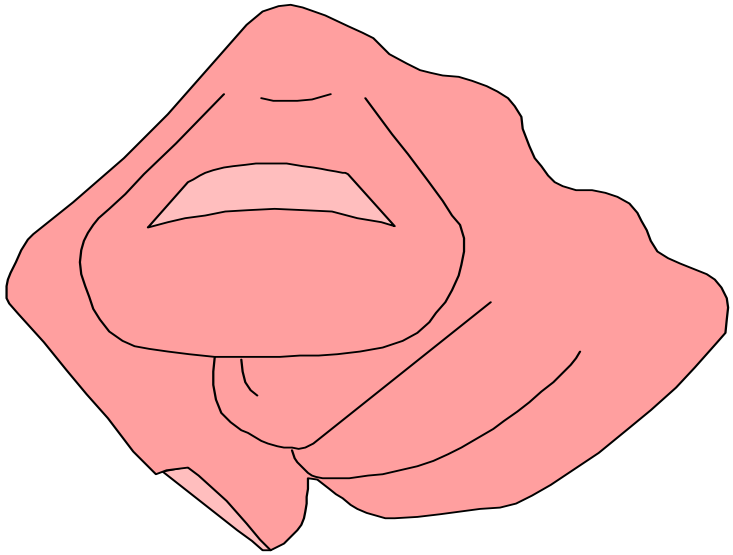
[*] FDA guide to inspections of high purity water systems (July 1993)

5. Summary

- General rules for the successful installation and operation of a water loop (PUW or WFI) are well known in the industry
- Technical factors, which are influencing the water quality, do also have a very high impact on investment cost
- Add. efforts, especially in welding documentation, do not essentially influence the water quality, but do have a very strong impact on cost
- Required qualification procedures and documentation should be clearly specified from the very beginning of a project to prevent misunderstandings between buyer and vendor

Many thanks for your attention !!

YOUR Questions and Comments



are now most welcome !!