Storage and Distribution of Pharmaceutical Water
Application of Ozone

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Objective

- Deliver Water to the Consumer (use points) without loss of Quality

Storage Tank

Weak Point of a Distribution System

- Stagnant conditions and areas of low flow rates
- Poor supply water quality

Microbial Control

Intermittent

- Chemical
  - Peracetic acid
  - Hydrogen peroxide
  - Sodium Hypochlorite
  - Formaldehyde
- Periodic Hot Water (80°C)
- Steam at 121°C (saturated steam)
- Hot water at 130...140°C (under pressure)

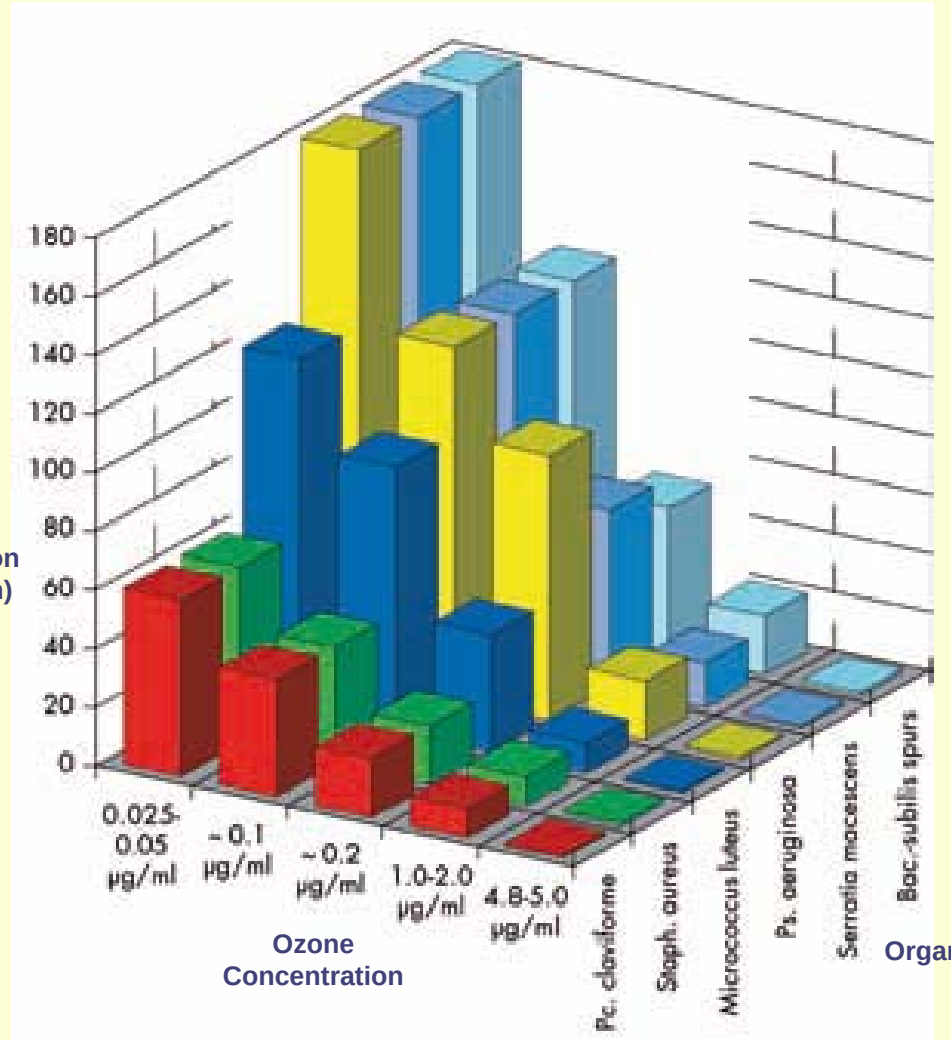
Microbial Control
Continuous

- Storage and distribution at ≥ 65°C
  ("Hot" Systems)
- Storage and distribution at 4 - 10°C
  ("Cold" Systems)
- Sanitization with Ozone

Ozone Properties

- Oxidation potential of 2.07 eV (second only to fluorine)
- 20 x stronger oxidant than chlorine
- No undesirable secondary by-products
- Generated at point of use
- Attack cell wall / membrane
- Typically 0.02 to 0.05 ppm in PW system
- Easily removed by UV light to <0.005 ppm

Ozone Disinfection Effectiveness



Microbial Control

PROCEDURES	ADVANTAGES	DISADVANTAGES
Periodic Sterilization / Sanitization with Steam at 121°C	• “no chemicals” • safety • well-proven and accepted • controllable by temperature	• installation costs • production stop • emptying of the systems necessary • sloped erection of the distribution system • work-intensive • no permanent protection
Periodic Sterilization / Sanitization with Chemicals: • Peracetic acid • Hydrogen peroxide • Sodium Hypochlorite • Formaldehyde	• efficient • simple handling • low investment costs	• chemicals • rinsing must be supervised • production stop • no permanent protection • time-intensive • damages to membranes / resins

Microbial Control

PROCEDURES	ADVANTAGES	DISADVANTAGES
Permanent sanitization at 65...85 °C	• “no chemicals” • high safety • accepted • easily controllable	• operating costs • costly cooling systems for cold points of use
Sterile filtration	• efficient • can be validated (Integrity Test)	• no protection for the whole system as this is a final filtration • investment costs • critical change of cartridges
UV-Units	• no chemicals • Installation and operating costs	• no absolute security • no water network protection • not efficient in vessels and tanks

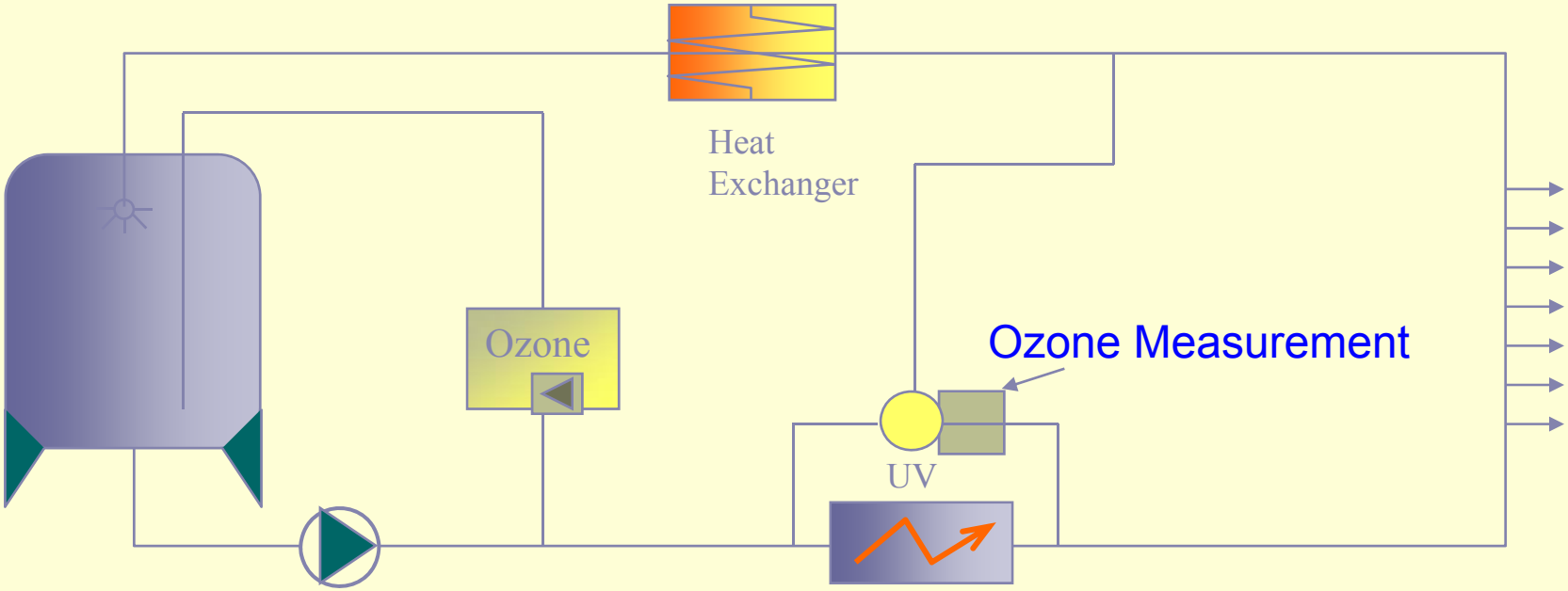
Microbial Control

PROCEDURES	ADVANTAGES	DISADVANTAGES
Electrolytic generated Ozone	• permanent protection of storage tank • periodic sterilization / sanitization • low maintenance costs • no contamination • protection of the water network • removal of pyrogens and TOC	• investment costs • material requirements • acceptance • destruction of the ozone may be necessary

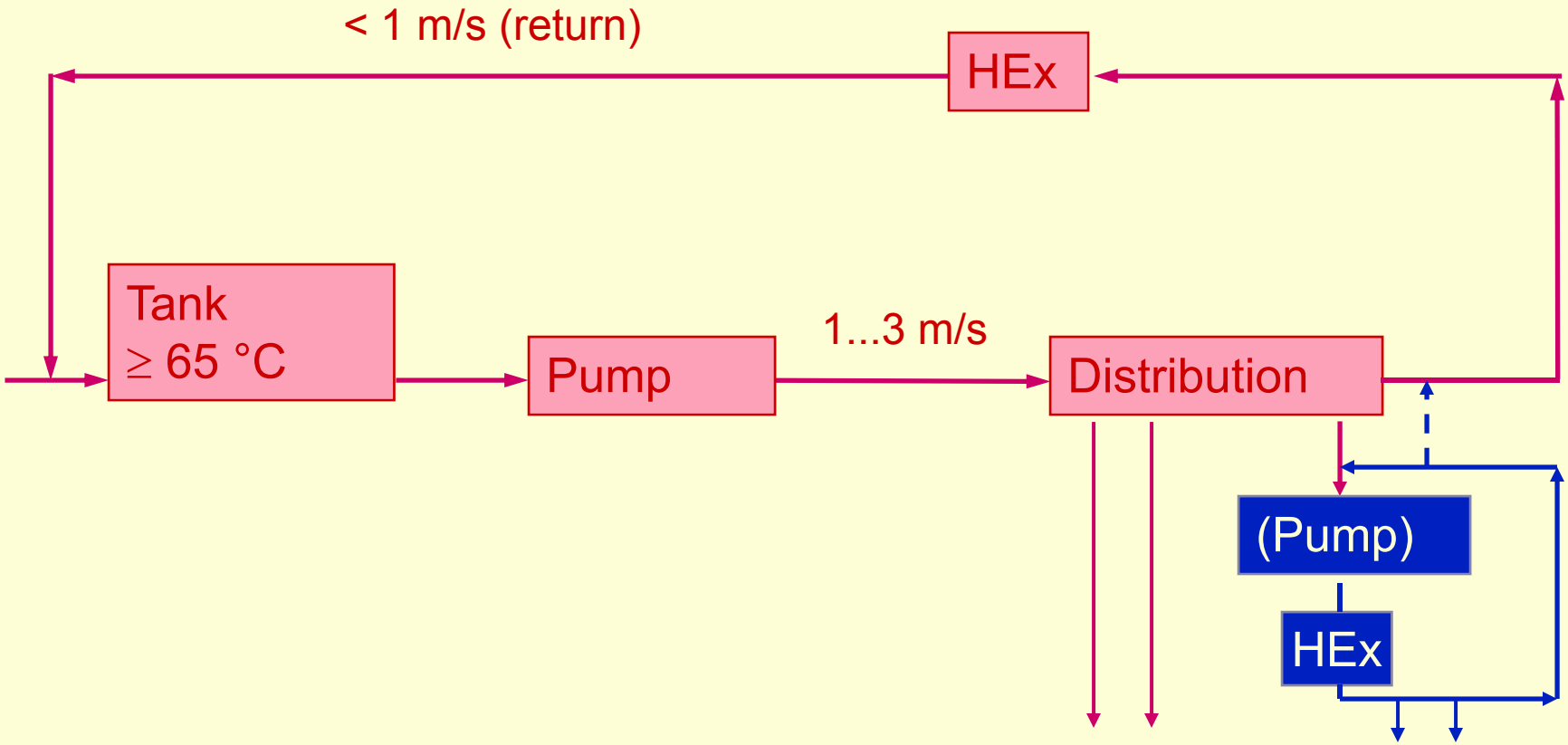
Purified Water System
Optimal Design Rules

- Size make-up plant as small as possible to ensure continuous operation
- Provide sufficient storage capacity to meet peak consumption
- Utilize continuous microbial control

Purified Water Loop
Ambient Distribution with Ozone



Purified Water Loop
Hot Distribution with Cold User



Operating Cost Comparison

for 100 m³ Purified Water / Day (~20 gpm average)

Sanitization at 80°C versus Ozone

Ozone:	0.1mg/l (100 ppb) = 10 g	
The production of 4 g ozone requires	approx.	1.5 kW
➔ Energy requirement	approx.	90kW-hr/day
Cost: **($0.125 per kW-hr)**		**11 $/d**

Sanitization and Cooling:		
Heating from	20 to 80 °C	
➔ Energy requirement	approx. 7000 kW-hr/day	
Cooling from	80 to 20 °C	
➔ Energy requirement	approx. 7000 kW-hr/day	
Cost: **($0.125 per kW-hr)**		**1750 $/d**

Distribution System

Rules of System and Point of Use Design

ISPE Baseline Guide Vol 4 "Water and Steam Systems" 2001:

A correct system design needs the characterisation of all user points:

- Flow rates
- Volumes
- Pressures
- Temperatures
- Simultaneous uses

Distribution System

Design Considerations

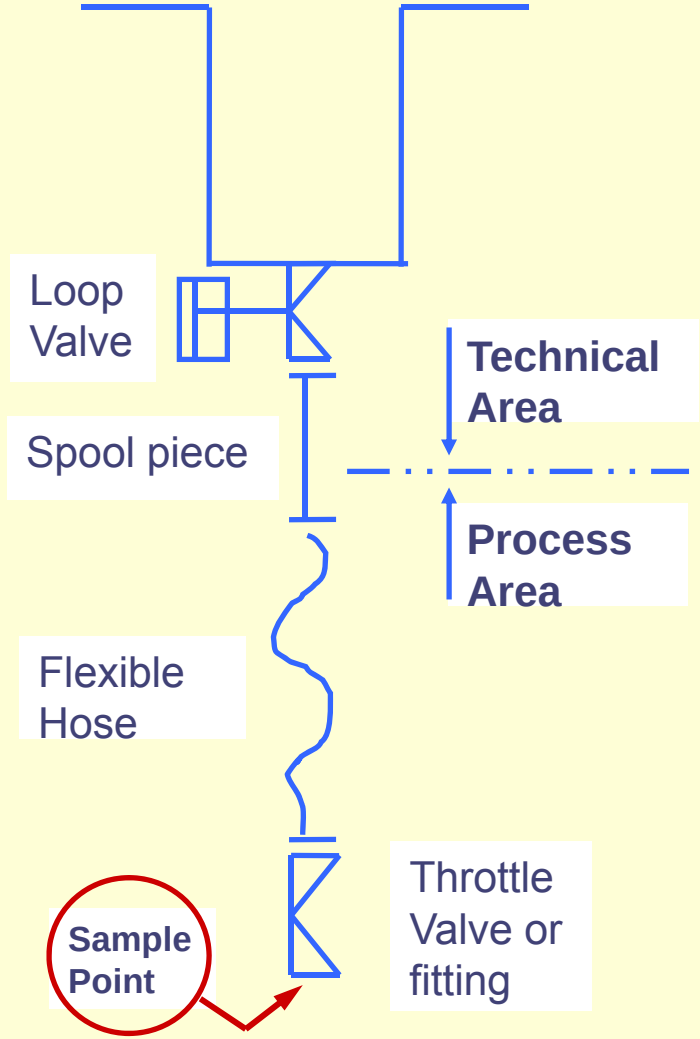
- Continuous turbulent flow
- Proper slope
- Avoid dead legs (≤ “6 D”; suggestion ≤ “3 D”)
- Smooth, clean surface for wetted parts
- Positive system pressure

Distribution System

Point of Use Design & Sampling

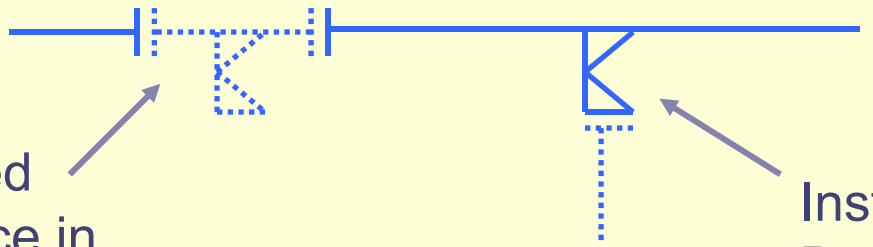
FDA guide to inspections of high purity water systems 1993:

"The sampling procedure for point of use sampling should reflect how the water is to be drawn, e.g. if a hose is usually attached then the sample is taken at the end of the hose. If the SOP calls for the line to be flushed before use of the water from that point, then the sample is taken after the flush".



Distribution System

Future Connections



Triclamped spool piece in main loop

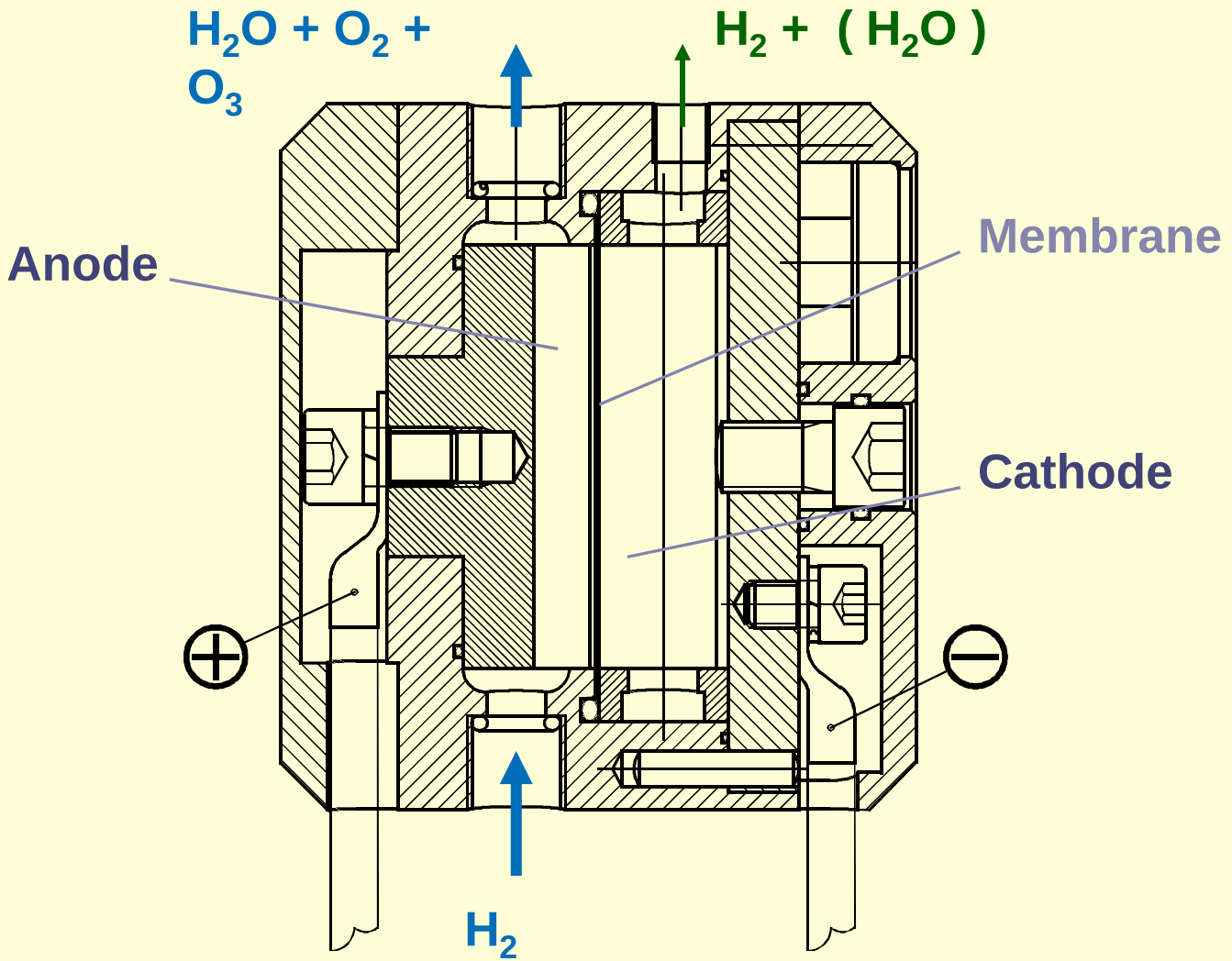
Installation of Zero Deadleg (ZDL) style valves

- Use of spool piece allows subsequent extension of loop, or installation of sub loops
- Already installed ZDL valves avoid loop system requalification after extension (→ production stop)

Electrolytic Ozone Production

- Electrolytic Process
- No Added Substances
- Low power consumption
- Reliable process
- Long term experience

Electrolytic Ozone Production



Electrolytic Ozone Production
Convincing Adantages

- **Dissolved Ozone produced directly from Purified Water**
- **No “Added Substances”**
- **Production of low ozone quantities in high concentration**
- **Chemical free operation**

Electrolytic Ozone Production
Convincing Adantages (cont'd)

- **Fully automatic and maintenance-free operation**
- **Control and Reduction of undesired water components is possible -- TOC, Biofilm, and Endotoxin (EU)**
- **Easily removed with no by-products**

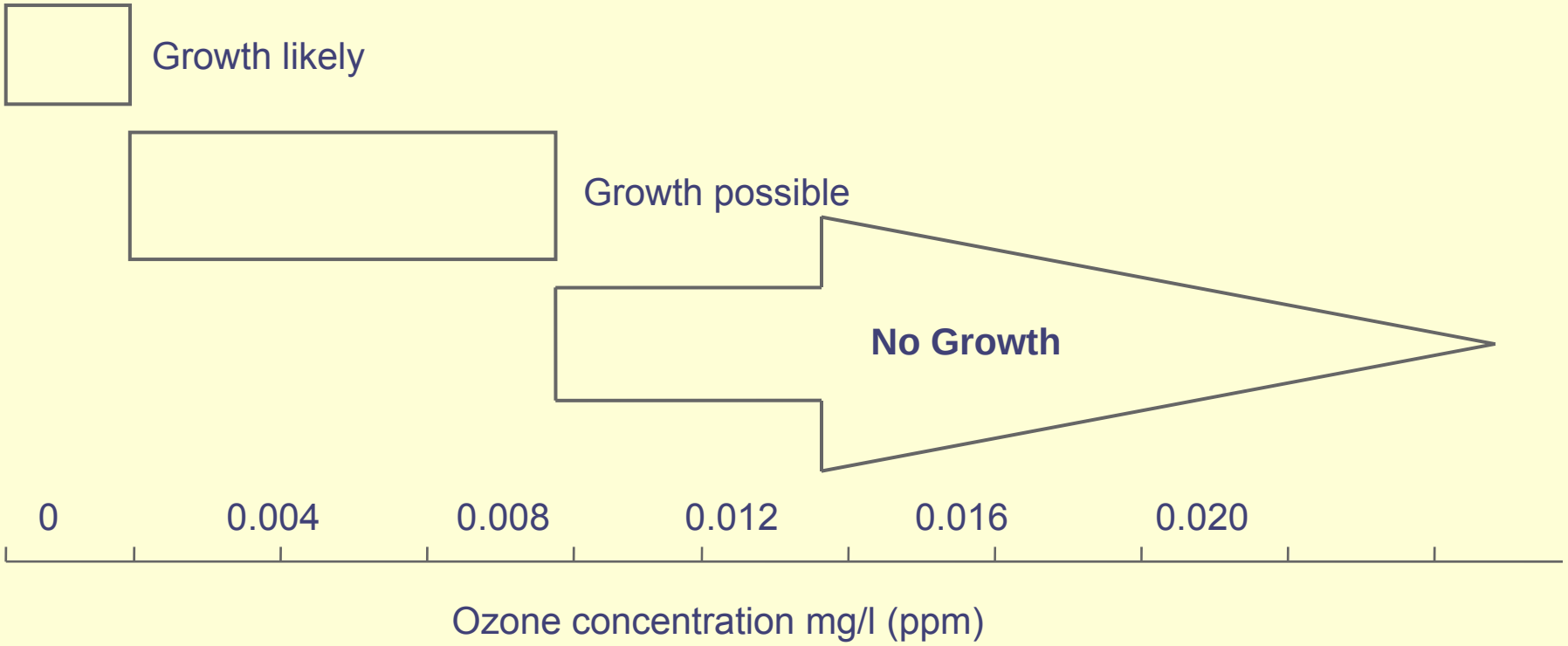
Ozone Application in PW Systems

- **All wetted parts must be ozone resistant (e.g. gaskets, filters)**
- **No need of a spray ball inside the storage tank**
- **Velocity is of less importance**
- **Biofilm formation is restrained**
- **The level of the storage tank is not critical**

Ozone Application in PW Systems (cont'd)

- **Temperature > 20 °C is less critical (but should not exceed 30°C**
- **Sanitary connections are not an absolute necessity**
- **Design of tank allows to reduce costs (pressure, safety devices etc.)**
- **Insulation is not required**
- **PVDF as distribution system is acceptable**

Ozone Concentration in PW systems



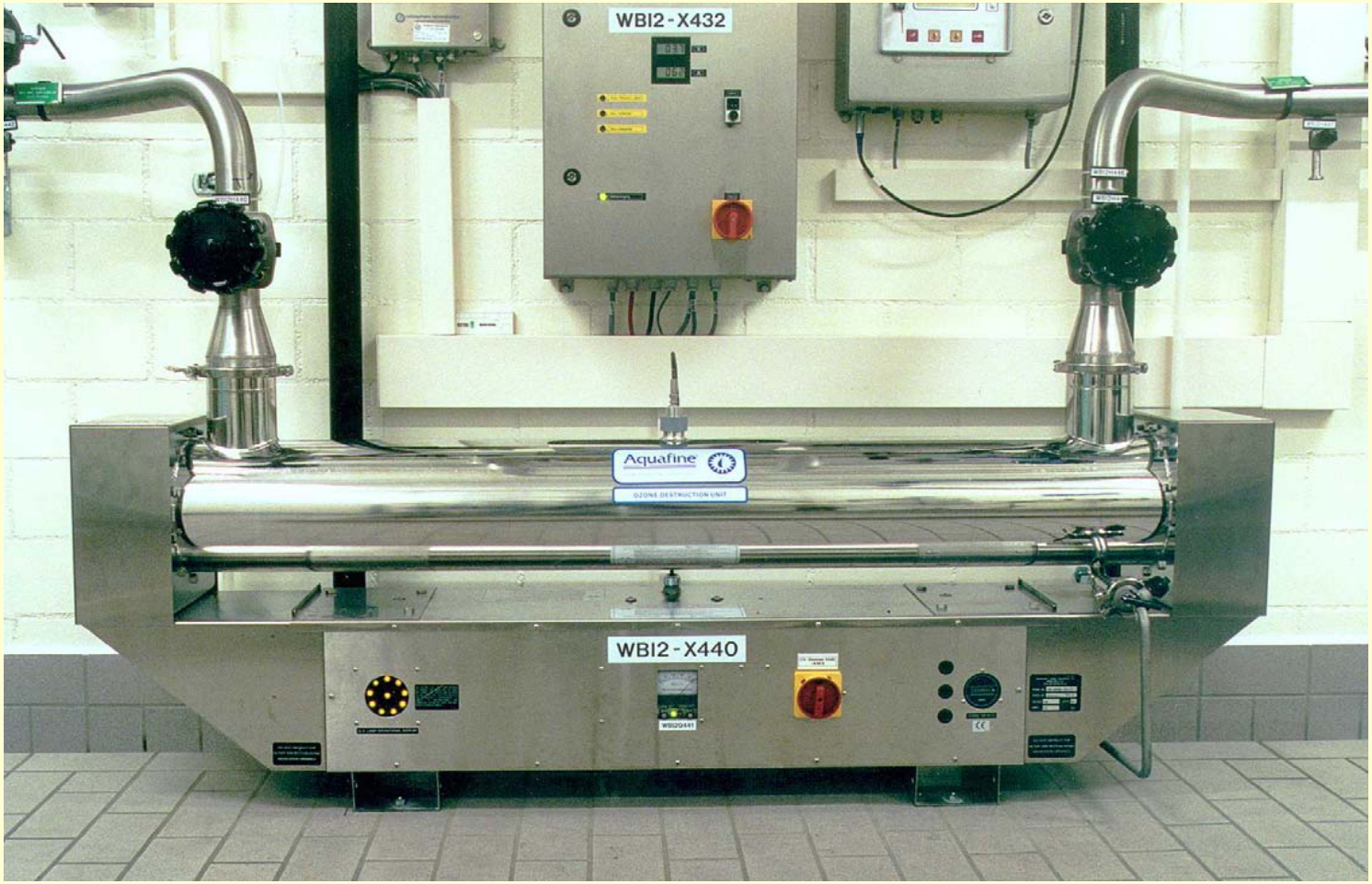
Hoffmann-La Roche (Swiss Pharma 1983)

Ozone Measuring Device

Absence and presence of Ozone should be proven

Ozone Destruction

By Ultraviolet Light



Compact Skid- Mounted System

- Variable speed-drive pump(s) for distribution system
- Electrolytic Ozone generator with following benefits
- UV unit for Ozone destruction at loop inlet
- Control cabinet
- Measurement of quality relevant parameters (Flow, Conductivity, Temperature, Ozone and TOC [optional])
- Heat exchanger for cooling [optional]

Customization Features

- One or two pumps (2x100%) with automatic change
- Pump can be flow or pressure-controlled
- Management of use points with interlocks (limit major use points at one time)
- SS or PVDF tubing
- Preferred suppliers can be utilized for pumps, Ozone and TOC intstruments…

Ozone Case Studies

Effect of Ozone on Biofilm

Biofilm in an old PVC distribution system (development building):

Counts	10...20,000	CFU/ml
Chemical disinfection:		no effect
Mechanical cleaning with air and NaOH 2% rinsing:		no effect

Introduction of ozone:
after one week results below 100 CFU/ml (constantly)

The plant is in operation since 1987 !

Ozone Case Studies

Effect of Ozone on Biofilm

Dialysis water system (SS 316 L) in a hospital:

Problems:

- Germs and EU: out of spec. (OOS)
- Distribution system over dimensioned (velocity < 20 cm/sec.)
- Endotoxins: > 1 EU/ml
- Germs: 200...1000 CFU/ml (no correlation with EU)

Solution: Sanitization with Ozone every night:

→ No OOS since more than 10 years !

Ozone Case Studies

Effect of Ozone on TOC

Plant 1 (IX) :

Raw water:	300 - 500 ppb
Ion exchanger:	peaks up to 850 ppb
UV 185 nm:	no effect !
Loop with ozone:	< 400 ppb

Plant 2 (RO-RO):

Raw water:	820 ppb
after 1st stage RO:	60 ppb
after 2nd stage RO:	40 ppb
After ozonization:	< 10 ppb

Plant 3 (RO-EDI):

Raw water:	820 ppb
After treatment:	18 ppb
Loop (PVDF):	< 5 ppb

Ozone Case Studies

Summary of Ozone Effects on TOC

- **Ozone has an impact on reduction of the TOC level in a system.**
- **However, Ozone should not be used as "TOC removal unit"**

Ozone is an agent to maintain the TOC on a low level in a system

Ozone Case Studies

Ozone Effects on Endotoxin

Plant 1 (IX):

Feed into the tank:	0.41	EU/ml
Distribution system:	< 0.06	EU/ml (Reduction rate > 85%)
Concentration of O**3**:	0.02	mg/l (20 ppb)

Plant 2 (RO-RO):

Feed into the tank:	0.08	EU/ml
Distribution system:	< 0.025	EU/ml (Reduction rate > 70%)
Concentration of O**3**:	0.08	mg/l (80 ppb)

Ozone Case Studies

Summary of Ozone Effects on Endotoxin (EU)

- **Ozone has an impact on reduction of EU level in a system.**
- **However, Ozone should not be used as "EU removal unit".**

Ozone is an agent to maintain the EU content on a low level in a system

Ozone Applications

- **Purified Water (PW)** — **yes**
- **Highly Purified Water (HPW; → low endotoxin)** — **yes**
- **Purified Water for hemodialysis** — **yes**
- **Purified Water in cosmetics, biotechnology and health care applications** — **yes**
- **Purified Water for general hygienic applications** — **yes**
- **Water for Injection (WFI)** — **(no)***

*** = none currently…**

Ozone…

"Green and Clean"

Thank you very much for your attention – Any questions?