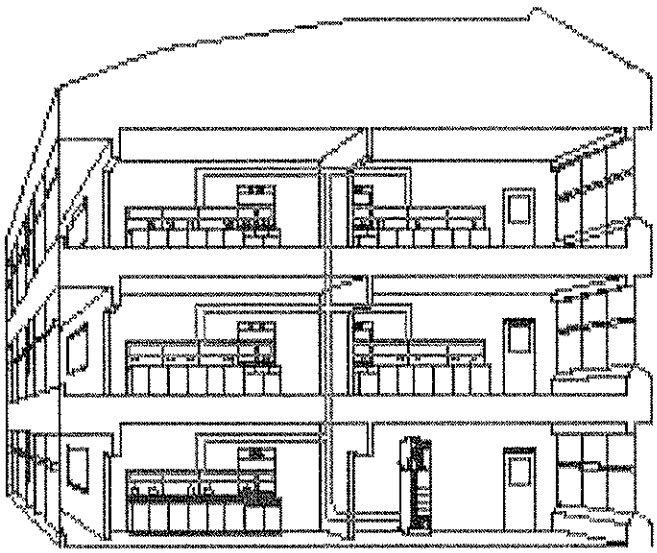
Total Pure Water Solutions... from Lab to Buildings



Renaud Bardon

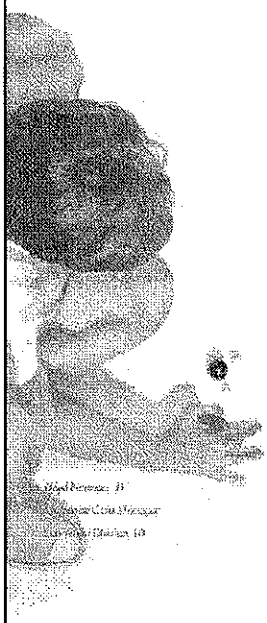
Singapore

MILLIPORE

Total Pure Water Solutions... from Lab to Buildings

~Agenda~

- Basics about Water Purification
- Design of Pure Water Solutions
- Large Flow Production Units – Elix and RiOs
- Total Water Solutions
- Validation
- Conclusion
- Case Studies and Applications



Millipore
Pure Water Solution Partner

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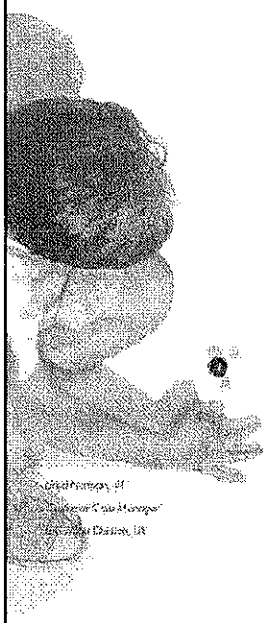

Basics about Water Purification

- **Water contaminants**
- **Monitoring of contaminants**
- **Water standards**
- **Water purification techniques**

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Water Contaminants

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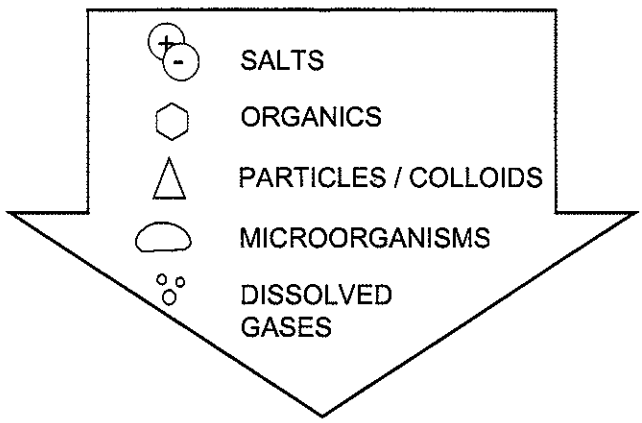
Tap Water Contaminants



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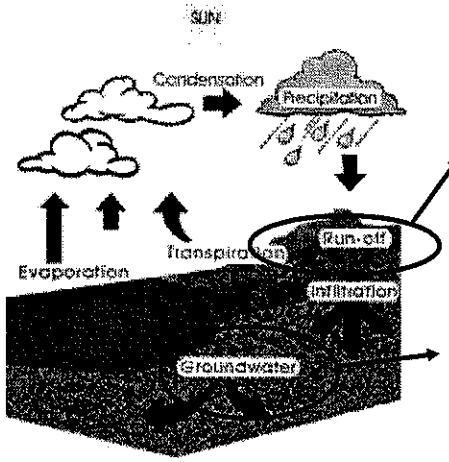
Ground & Surface Water



Surface Water
- Higher in biological material.
- Higher in particulates
- Lower in dissolved ions

Ground Water
- Higher in dissolved ions
- Low in particulates
- Low in biological Material

Ground & Surface Water

- Ground Water : from wells. Therefore, has usually a high concentration of ionic contaminants(TDS), but a low organic contaminants concentration. Typical problem: scaling (CaCO3) and plugging (particulates). There are exceptions (source water)
- Surface water : from lakes and rivers. Has usually a low concentration of inorganic contaminants (20 to 40 µS/cm in Scottland, Norway), but a high organic contaminants concentration (decay of leaves after fall). Typical problem: TOC and fouling.
- Tap water companies use both sources to produce potable water… and may switch from one to another without warning in some regions.

Water Contaminants Monitoring

- **Ions Detection by Resistivity**

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Conductivity of Water

$$\chi = F \Sigma C_i Z_i u_i$$

- χ: Conductivity (Siemens/cm)
- F: Faraday
- C_i: Concentration of each ionic species (moles/ml)
- Z_i: Valence
- u_i: Mobility $V^{-1}.cm^2.s^{-1}$

Higher temp Means Higher Mobility

i.e. 25°C

Resistivity

$$R = 1/\chi$$

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Ultrapure Water Theoretical Conductivity

In theoretically pure water the only ionic species are H+ and OH- coming from the dissociation of water

$[H^+] = [OH^-] = 10^{-7}$ eq/l (or 10^{-10} eq/ml)

the values of equivalent conductance Fu given by the tables are :

Fu H^+ = 350 Ω^{-1} cm ^{2} at 25°C

Fu OH^- = 200 Ω^{-1} cm ^{2} at 25°C

The Calculation gives :

for theoretically pure water : χ=0.055µS/cm at 25°C

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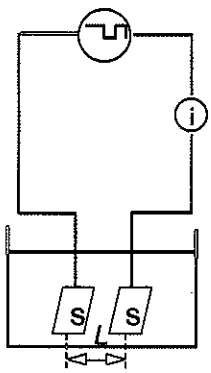
Conductivity or Resistivity meter



- AC Low frequency <100 Hz to limit the phenomena of resistance parasites
- Voltage < 1.2 V to avoid water split reactions at the surface of electrodes
- Cell Constant = L/S
- Low cell constant = better accuracy: higher signal and lower interferences

$$R = V/I \qquad R = \rho . L/S$$

Cell Constant : L/S
R = Resistance
ρ = Resistivity

$$\rho = \frac{V}{I.L/S}$$

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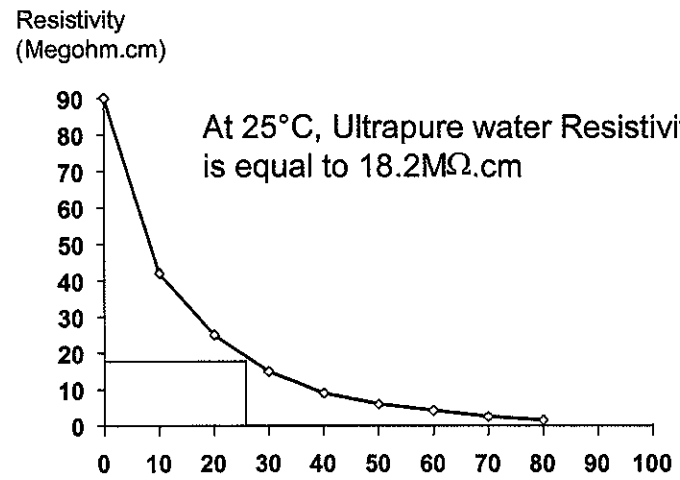
S = Surface Area

Ultrapure Water Resistivity = f (T)



At 25°C, Ultrapure water Resistivity is equal to 18.2MΩ.cm

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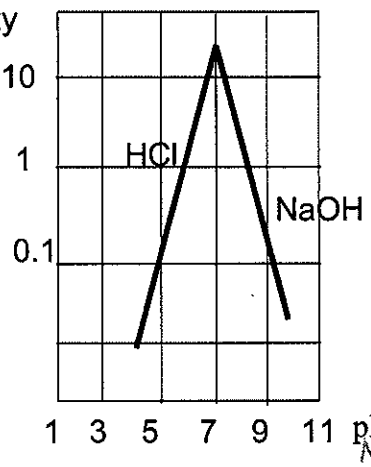
Ultrapure Water : pH and resistivity

Influence of trace levels of HCl and NaOH on the resistivity of water.



Conclusion: the pH of Ultrapure Water (R = 18.2 MΩ.cm) cannot be different of 7.0

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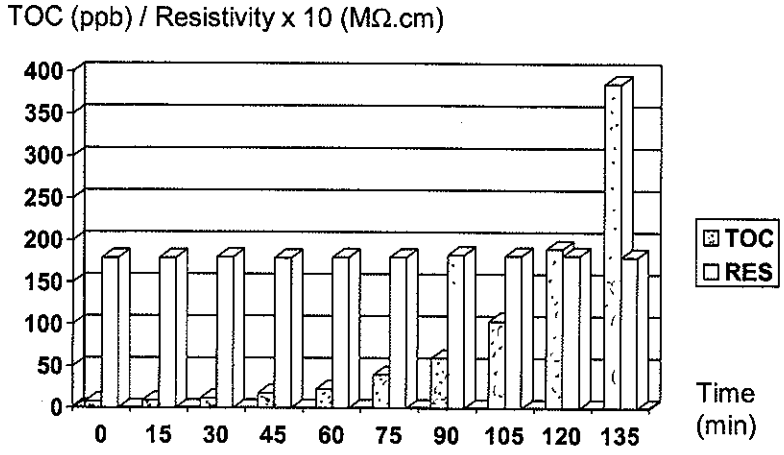
$H_2O \xrightarrow{CO_2} H^+ + HCO_3^-$ (Acidic)

∴ Must use water right away

Resistivity is not enough



Organic breakthrough occurred with no resistivity change

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Water Contaminants Monitoring

- **Organic Substances Detection by TOC**

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TOC in Water

- TOC = Total Oxidizable Carbon
  Total Organic Carbon
- Tap water, the 'raw material' used to produce pure water for laboratory applications may contain many different oxidizable carbon substances, mainly dissolved.

Example : Methanol

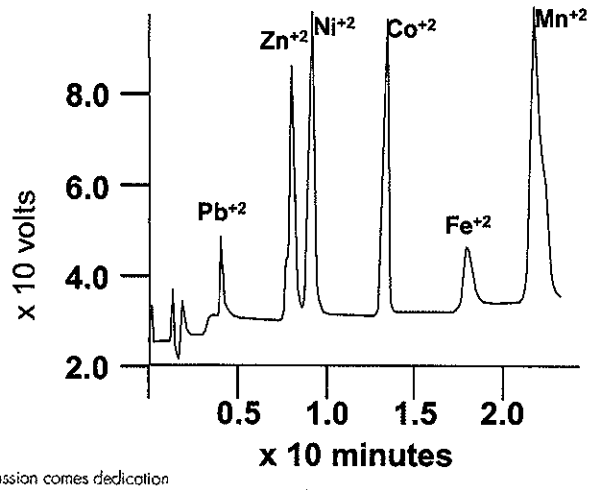
Methanol (CH_3OH) has a molecular weight equal to : (3 x 1) + (12) + (16) + (1) = 32

What will be the TOC level generated by a 50 ppb methanol concentration in pure water ?

The carbon content of methanol is
12 / 32 = 0.375
Therefore , 50 ppb methanol is equal to
50 x 0.375 = 18.75 ppb TOC

Ion Chromatography (1)

Buffers Prepared with Standard Ultrapure Polisher



Method: Transition metal analysis using dynamically coated reverse phase method with trace enrichment

Column: Waters Delta Pak C (5mm)

Eluent: 2 mM sodium octane sulfonate/ 50 mM tartaric acid/ 2% acetonitrile; pH 3.4 NaOH

Flow rate: 1.0 ml/min

Detection: Post-column derivatization with PAR

Detector: Waters M484 UV/visible at 520 nm

Injection Volume: 100mL

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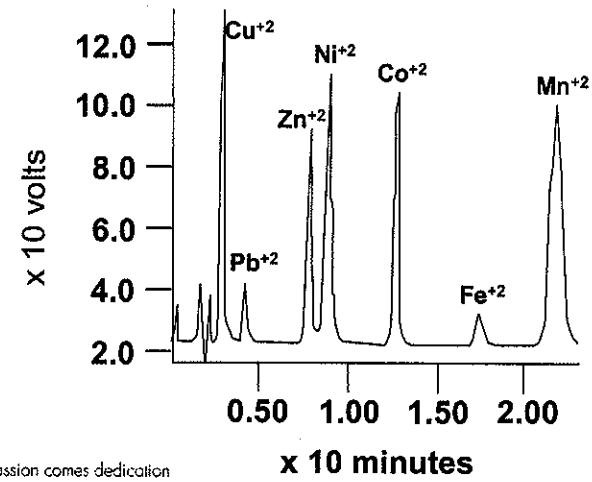
Ion Chromatography (2)

Buffers Prepared with Milli-Q Low Organics Water



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Detection: Post-column derivatization with PAR

Detector: Waters M484 UV/visible at 520 nm

Injection Volume: 100mL

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Ion Chromatography (3)

- Copper is weakly bound to the column
- In the first experimentation, copper was probably shielded by organics and did not bind to the column.
- In the second experimentation, low TOC water was used. The copper was bound to the column.
- Conclusion: the same method gives different results when low TOC water is used.

Laboratory Water Standards

Water Types & Applications

- **Type III** : glassware rinsing,heating baths and autoclaves filling, feed to Type I Lab Water System
- **Type II :** buffers, pH solutions and microbiological culture media preparation ,clinical analysers and weatherometers feed, preparation of reagents for chemical analysis or synthesis
- **Type I :** HPLC mobile phase preparation; blanks and sample dilution in GC, HPLC ,AA , ICP-MS and other advanced analytical techniques ; preparation of buffers and culture media for mammalian cell culture, IVF, reagents for molecular biology...

Table of Specifications for water types

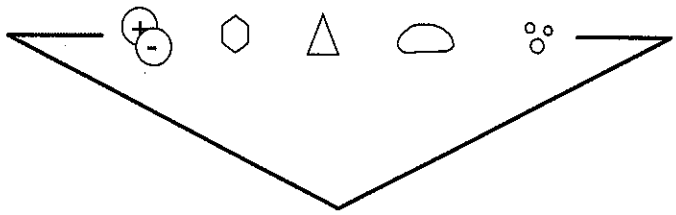
Contaminants	Parameter (units)	Type 1	Type 2	Type 3
Ions	Resistivity (MΩ·cm)	> 18.0	> 1.0	> 0.05
Organics	TOC (ppb) Pyrogens (EU/ml)	< 10 < 0.001	< 50 NA	< 200 NA
Particulates	Particulates > 0.2 µm (units/ml)	< 1	NA	NA
Colloids	Silica (ppb)	< 10	< 100	< 1000
Bacteria	Bacteria (cfu/ml)	< 1	< 100	< 1000

USP XXVII - Purified Water

- Conductivity
  - < 1.0 µS/cm from 10 to 15°C
  - < 1.1 µS/cm from 15 to 20°C
  - < 1.3 µS/cm from 20 to 25°C
  - < 1.4 µS/cm from 25 to 30°C
- TOC < 500 ppb
- pH > 5.0 and pH < 7.0
- Bacteria < 100 cfu/ml (FDA requirement)

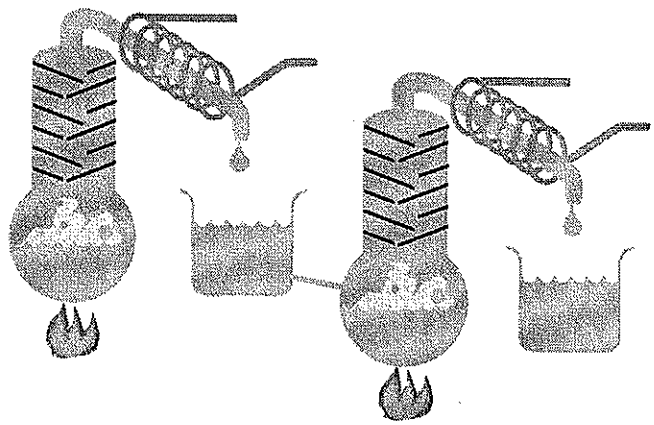
Water Purification Techniques

Water Purification Techniques



Contaminants Removal By							
Still	DI	EDI	RO	UF	MF	AC	UV 254 185

Distillation (Single/Multiple)



Distillation

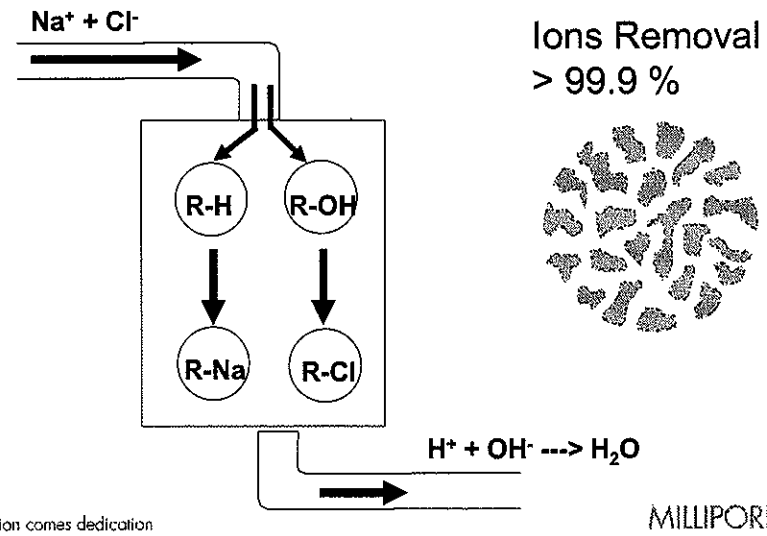
Advantages

- Removes a large percentage of all types of contaminants
- Produces water with resistivity between 0.2 and 1 Megohm.cm
- Average investment
- Well known and perceived as easy to operate

Disadvantages

- Not all contaminants are removed and several are generated during the process
- No control of water quality
- High operating costs due to electric heating (0.8KW/L) and water cooling (15 L/L)
- Regular maintenance (acid cleaning) or pretreatment (DI) is actually required to ensure optimum performance

Deionisation (DI) with Mixed Bed Resins



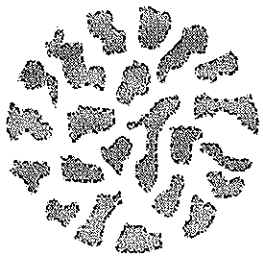
Ions Removal
> 99.9 %

Only remove ions.

Desionisation (DI)

Advantages

- Effective at removing ions (Resistivity : 1 - 10 Megohm.cm)



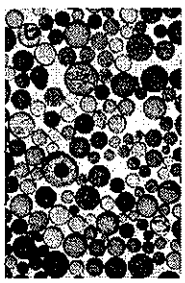
Disadvantages

- Does not eliminate particles, organic materials or microorganisms.
- Limited capacity depending on binding sites density and accessibility : requires good quality feed water to prevent premature exhaustion.
- Capacity related to flow rate

Regenerable DI

Advantages

- Simple to install
- Limited investment
- Regenerable



Disadvantages

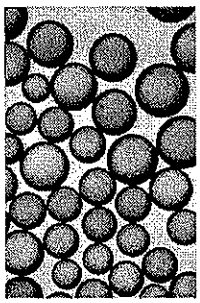
- Standard exchange : origin of resin unknown.
- Multiple regenerated resins generate particles and organics from damaged resin beads, and promote bacteria development
- High running costs : regeneration/ transportation
- Variable water quality: imperfect regeneration, additional contamination (damaged resin beads, bacteria).

Resin beads will crack over time and affect water quality

Single use (virgin) DI

Advantages

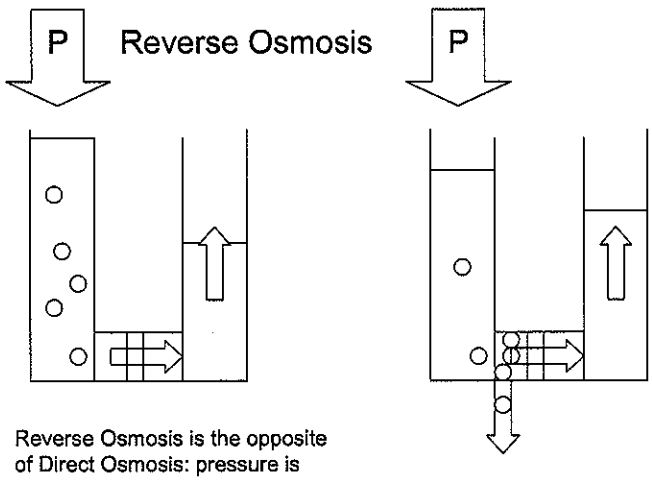
- Simple to install
- Limited investment
- Little contaminants addition if properly the material is properly selected.



Disadvantages

- Single use = high operating costs. Therefore its usage is limited to polishing applications.
- Requires good quality feed water to prevent premature exhaustion.

Reverse Osmosis



Reverse Osmosis is the opposite of Direct Osmosis: pressure is applied on the solution, and pure water goes through the semi-permeable membrane.

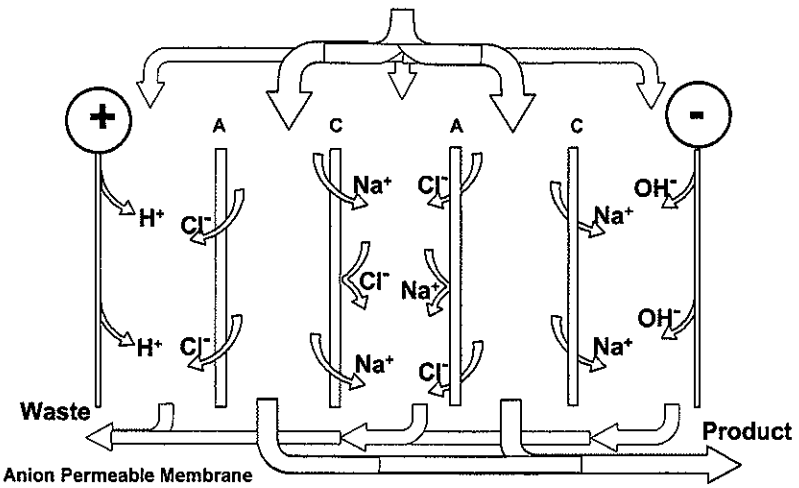


Reverse Osmosis Benefits

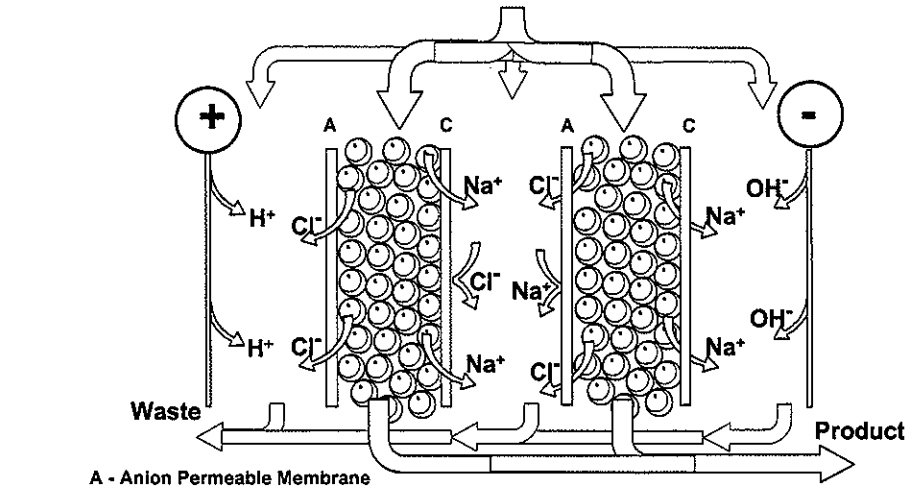
- Removes a fair percentage of all types of water contaminants (ions,organic,pyrogens, viruses,bacteria, particulate,colloids)
- Low operating costs due to low energy needs
- No need for strong acid and bases cleaning ; minimum maintenance
- Safe to use in a laboratory (no heating parts)
- Good control of operating parameters (inlet and outlet conductivity, feed water pressure).
- Ideal protection for ion-exchange resin polishing: removes a large part of the ions and eliminates the particulates, organic substances and colloids that could cause fouling of the ion-exchange beads.

1°C difference in temp will affect 3 % of flowrate of water.

Product & Waste Flow Paths



Ion-Exchange Resin in Product Channel



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Resin is used to speed up the process.

EDI Module : Scaling Risk

pH	Ca^{+2} (ppm)	HCO_3^- (ppm)
7	3600	10
8	360	10
9	36	10
10	3.6	10
11	0.36	10
12	0.036	10

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Higher PH will be more rigidly to cause Scaling

Scaling due to high pH at cathode

OH^- Generated at Cathode

↓

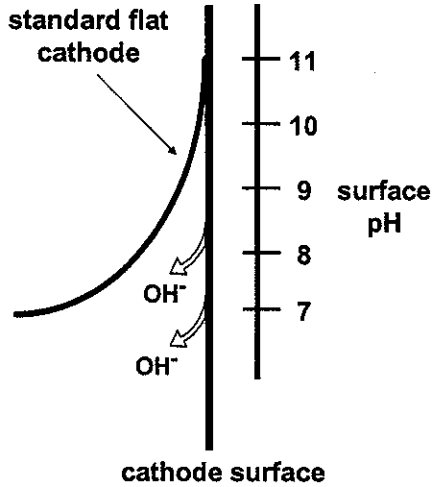
High Local Surface pH

↓

High Scale Potential

↓

SOFTENER NEEDED
Most Locations



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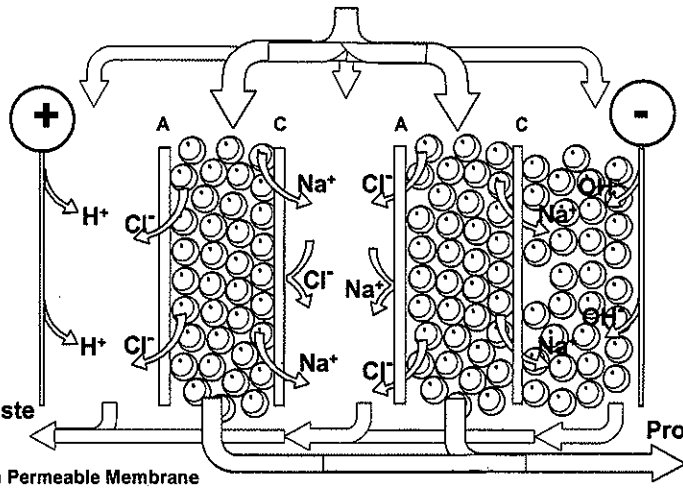
Conductive Carbon Beads Effect on pH



A - Anion Permeable Membrane
C - Cation Permeable Membrane

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Carbon Beads: less steep pH gradient

High Surface Area Cathode = Generation of hydroxyls in a larger volume

↓

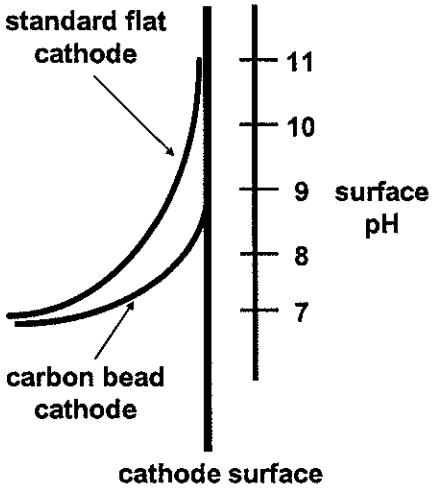
Reduces Local Surface pH

↓

Reduces Scale Potential

↓

NO SOFTENER NEEDED



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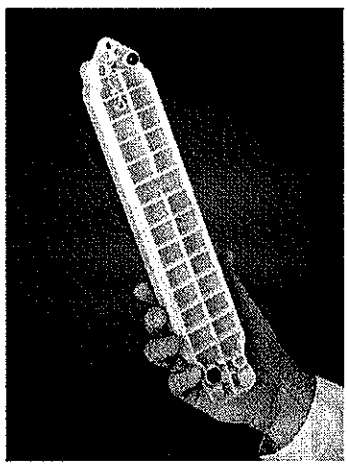
ElectroDelonisation (EDI) Module

High Tolerance to Calcium
No softener required

New and Clean Design
Improved Performance

Compact Module
Compact System



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Electro-deionisation (EDI)

Advantages

- Very efficient removal of ions and small MW charged organic (R> 5 Megohm.cm)
- Low energy consumption
- High water recovery
- Low operating cost
- Low maintenance
- No particulates or organic contamination (smooth, continuous regeneration by weak electric current)
- Moderate investment

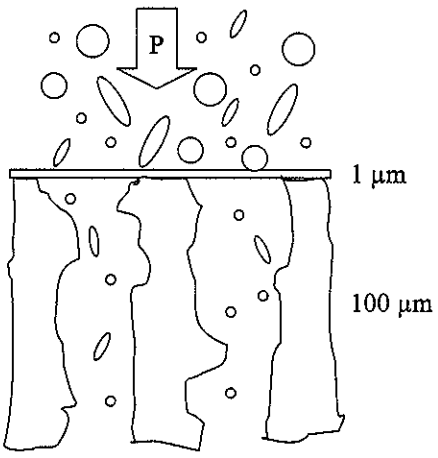
Disadvantages

- Requires good quality (RO) feed water to prevent plugging (particulates), fouling (organic, colloids) of ion-exchange resin beads and scaling at cathode.
- CO2 not totally removed if at high level in feed water.

Ultrafiltration

- Ultrafilters are asymetric membranes, sometimes composite
- Under pressure,small size molecules go through the membrane,whereas molecules larger then the NMWL are retained

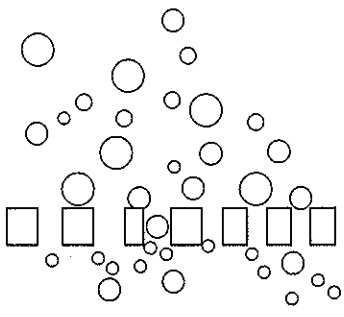
Organics with MW > NMWL : Rejection > 99 %



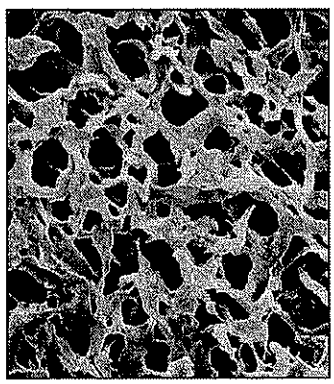
Ultrafiltration

- Effective removal (>99%) of all organic molecules with molecular weight above the NMWL. Very efficient at removing pyrogens and viruses as well as particles.
- No risk of scaling ; limited risk of fouling.
- Low use of water and energy
- Low maintenance ; procedures well documented / accepted.
- Almost no rejection of ions, gases and low molecular weight organics (tightest UF membranes have a 1,000 dalton cut-off

Membrane Microfiltration



Screen filter
100 % Removal



Durapore
Membrane SEM

Membrane Microfiltration

Advantages

- 100 % removal of all contaminants (particulates, bacteria)larger than pore size. Integrity test available
- Sterilizing filtration (0.22 um membranes - LRV > 7)
- Minimum maintenance : simply replace when required.
- High flow rates are achievable at low pressure
- Efficiency independent of flow rate.

Disadvantages

- Minimum effect on other contaminants
- Surface retention : may be subject to fouling/ plugging

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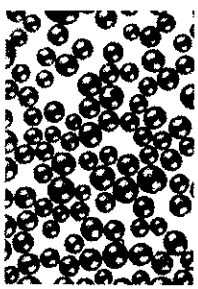
Activated Carbon

Total surface area : 1000m²/g

- Removal of chlorine from tap water by reduction
- Removal of organics by adsorption



Natural



Synthetic

Activated Carbon

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cleaner & with bigger surface area than natural type.

Activated Carbon

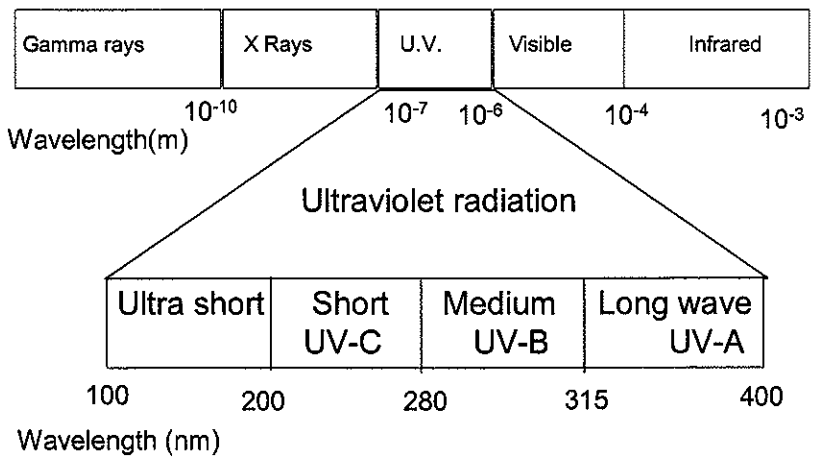
Advantages

- Effective removal of a large range of organic substances (even of low molecular weight) by non specific binding (Van der Waals forces)
- Large capacity due to high developed surface

Disadvantages

- Very little effect on other contaminants (except some particulates removed by depth filtration)
- Once all active sites are occupied, an equilibrium is established and organics are released.
- Bacteria may develop after several months.
- Efficiency depending on flow rate

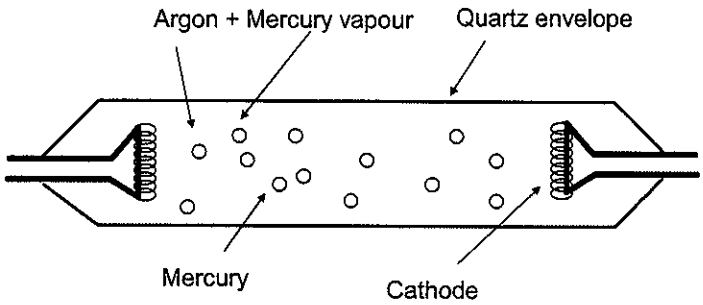
UV: Electromagnetic Spectrum



$E = h\nu$

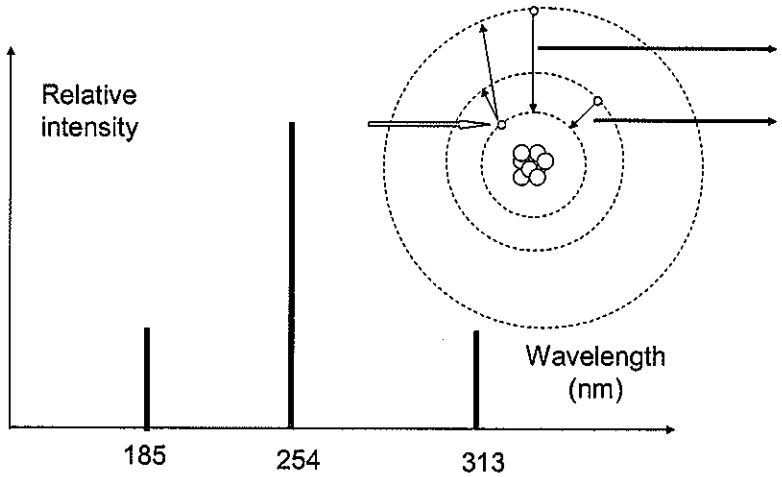
$\nu \propto \frac{1}{\lambda}$

Low Pressure Mercury Vapour Lamp



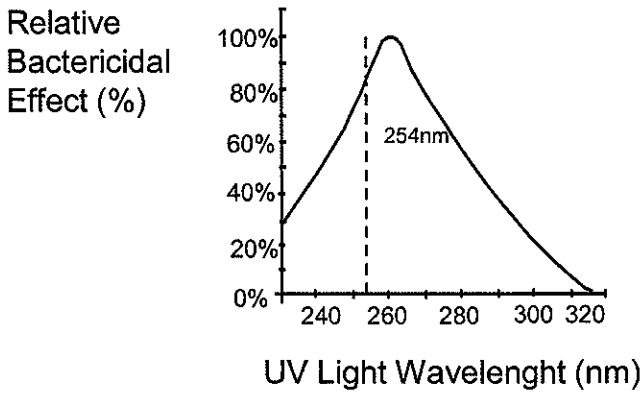
Schematic of a low pressure mercury vapour lamp
with hot electrodes

U. V. Technology



Emission of a low pressure mercury lamp.

Germicidal Action (254 nm)



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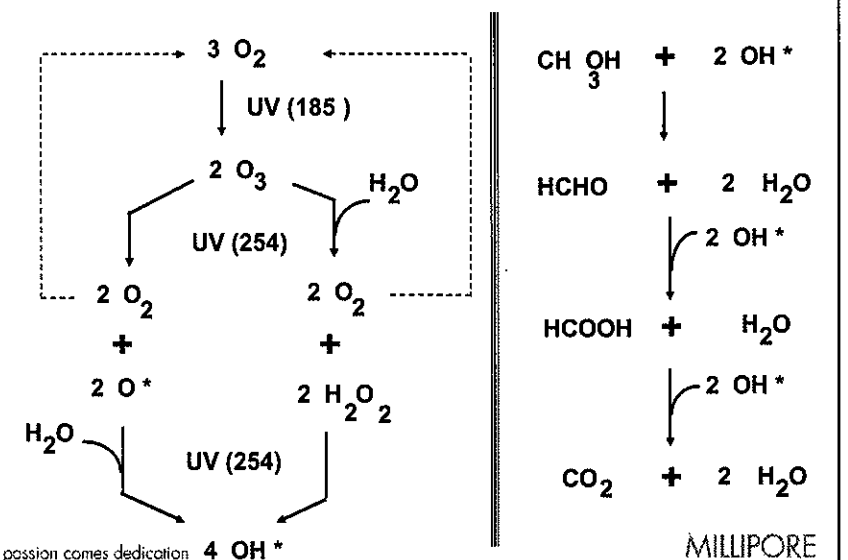
UV Action on Organic Contaminants



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UV Technology (185 + 254 nm)

Advantages

- Conversion of traces of organic contaminants to charged species and ultimately CO2 (185 + 254)
- Limited destruction of micro-organisms and viruses (254)
- Limited energy use
- Easy to operate

Disadvantages

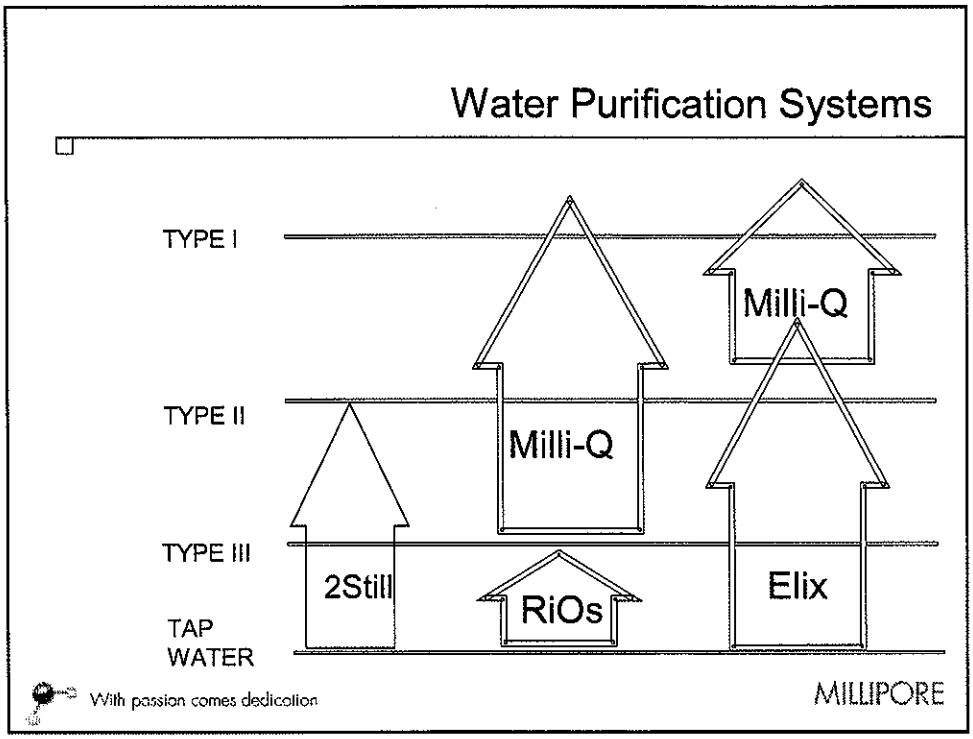
- Polishing technique only: may be overwhelmed if organics concentration in feed water is too high
- Organics are converted, not removed.
- Limited effect on other contaminants
- Good design required for optimum performance.

Technologies & Contaminants Removal

	STILL	DI	RO	UF	MF	AC	UV
IONS							
ORGANICS							
PARTICLE COLLOIDS							
BACTERIA							
GASES							

Contaminant still 100% present (not removed)

Contaminant completely (100%) removed


Water Purification Systems
TYPE I
TYPE II
TYPE III
TAP WATER
Milli-Q
Milli-Q
2Still
RiOs
Elix
With passion comes dedication
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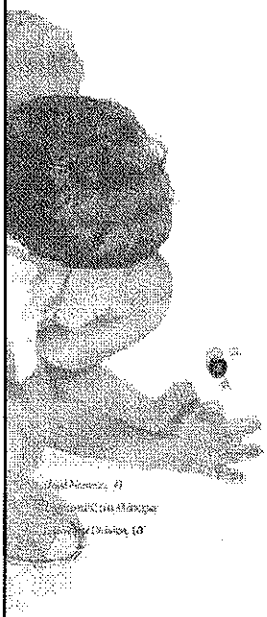

Design of pure water solutions

- **Laboratory Bench Systems**
- **Larger Flow Purification Systems**
- **More than systems a solution**
- **Typical central system**
- **Millipore Partner of choice**
- **Support at each project step**
  - Product design
  - Complete solution design

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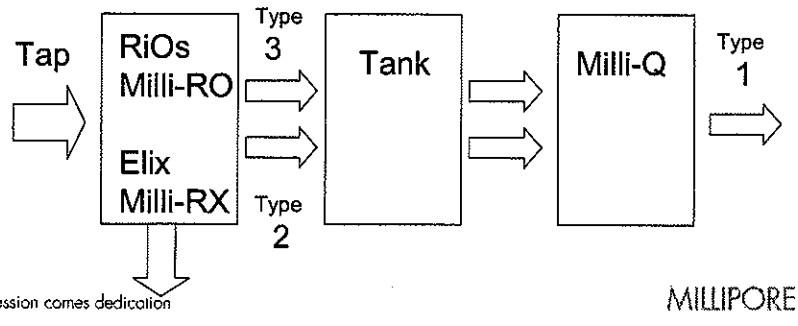
Millipore Water Systems

- Type 3 : Water Production: RiOs and Milli-RO
- Type 2 : Water Production : Elix and Milli-RX
- Storage of Type 3 and Type 2 Water
- Type 1 : Water Production : Milli-Q,Direct-Q,Simplicity



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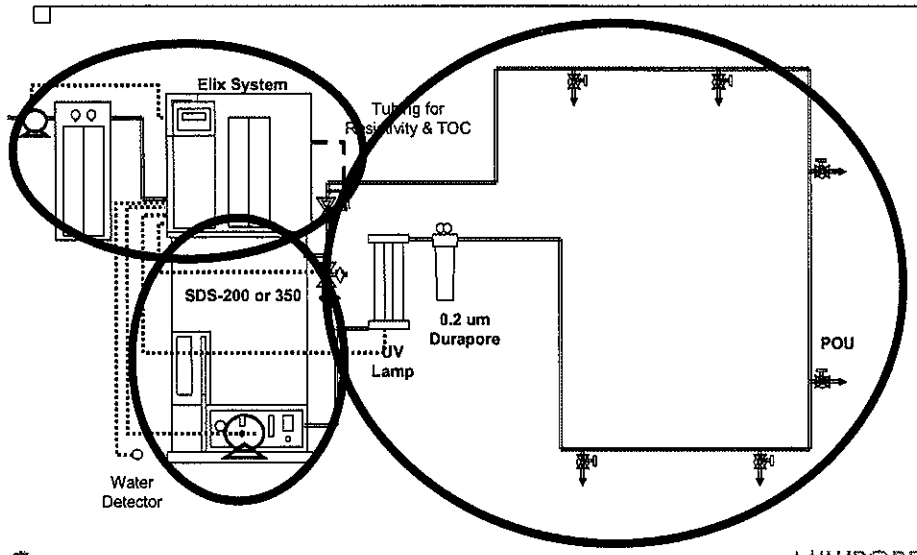
Central System Typical Architecture



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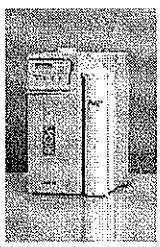
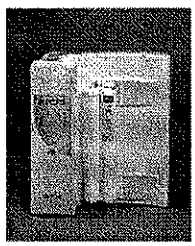
Type 3 : RiOs and Milli-RO

- Purpose : optimum controlled production of type 3 water
- Technologies: Pre-treatment and Reverse Osmosis
- Systems: RiOs (3,5,8 and 16 L/hour) and RiOs (30, 50, 100, 150 and 200 L/hour)
- Applications : Glassware washing, Autoclaves Feed, Heating baths feed, Feed of Type 1 water systems





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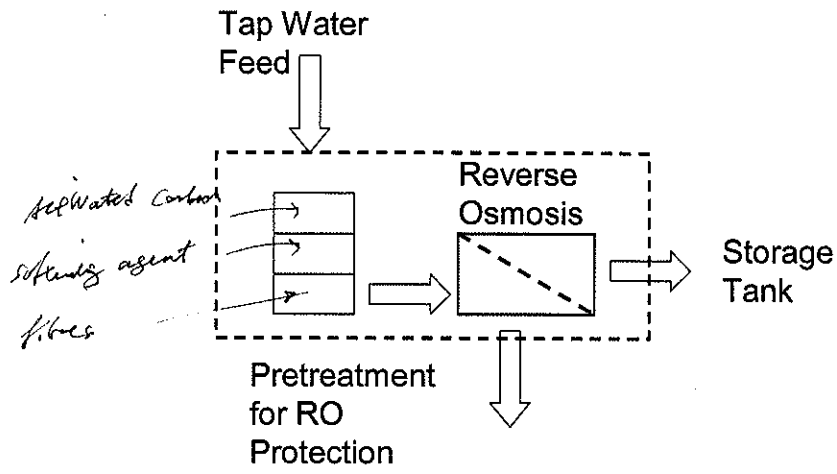
RiOs and Milli-RO Technologies



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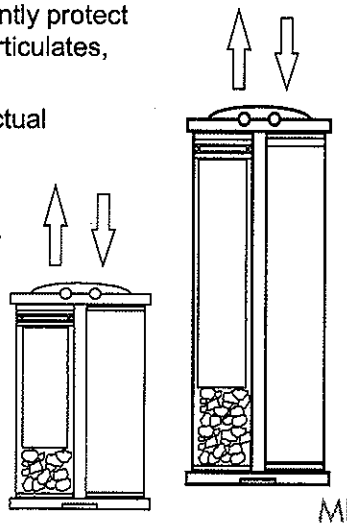
RiOs Pretreatment: Progard 1 and 2

Three components to efficiently protect the RO cartridge against particulates, chlorine and CaCO3

Pack exchange based on actual system operating conditions

Two sizes adapted to different feed water qualities

BENEFITS : lower costs, optimum water quality , peace of mind.



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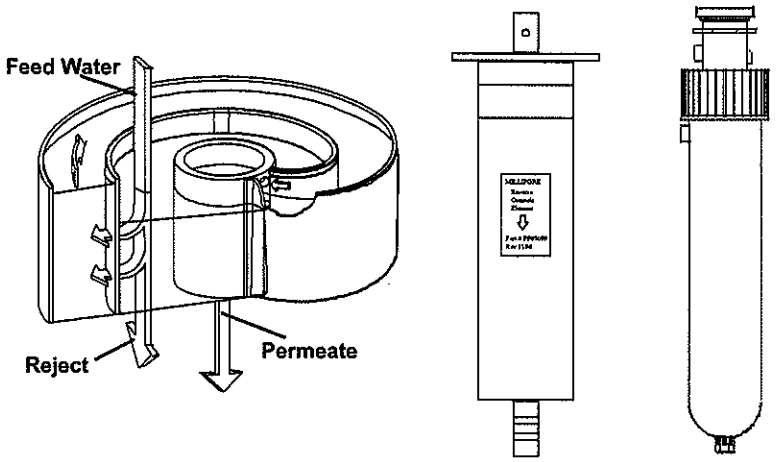
Reverse Osmosis :Spiral Cartridge



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RO Membrane damaged by CaCO3

RO Membrane treated by methylene blue to view the damages caused by CaCO3 deposits



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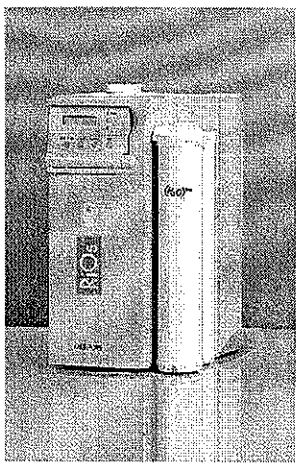
RiOs Systems



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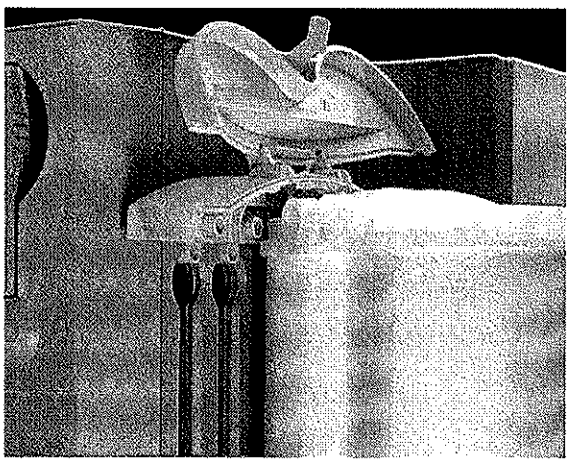
Easy Operation: Progard Replacement



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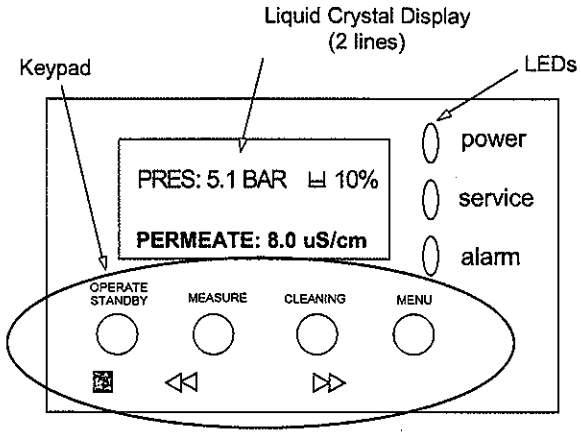
RiOs Display : Complete Control



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Data Availability trough RS 232 :

A Quality Report can be printed every day with the feed water temperature and conductivity, and the permeate conductivity, and attached to the notebook.

```
*****************
*  MILLIPORE    *
*****************

SYSTEM :  RiOs 5
SERIAL N: XXXXXXXXXX
PROGR.VERSION : V2.01

   * QUALITY REPORT *

DATE :                JUN-19/98
USER NAME :           Dr Rossi

TEMPERATURE :         15.5  C
RO FEED  :            476 uS
PERMEATE :            5.6 uS
```

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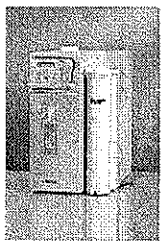
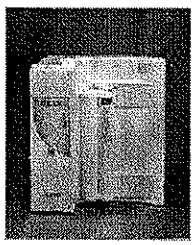
Type II : Elix

- Purpose : optimum controlled production of type 2 water
- Technologies: Pre-treatment, Reverse Osmosis, EDI
- Systems: Elix (3,5 and 10 L/hour)
  Elix (20, 35, 70 and 100 L/hour)
- Applications : Microbiological media,buffer and reagent preparation, feed to instruments (weatherometers, humidifiers, clinical analyzers...) Purified water (USP)





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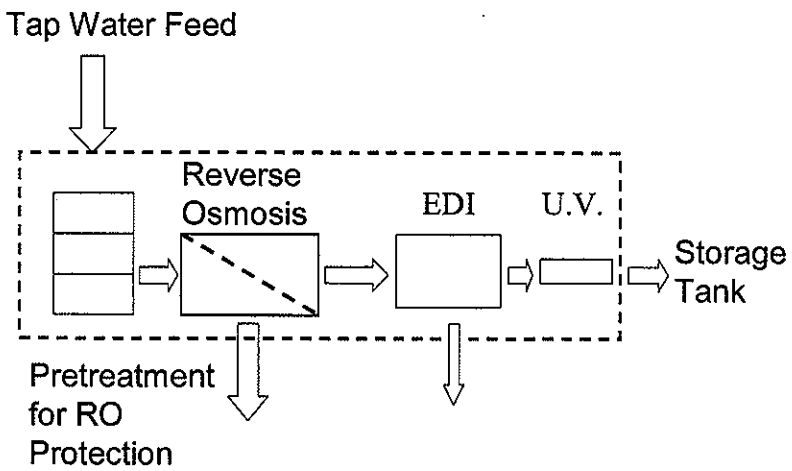
Elix



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Elix Systems

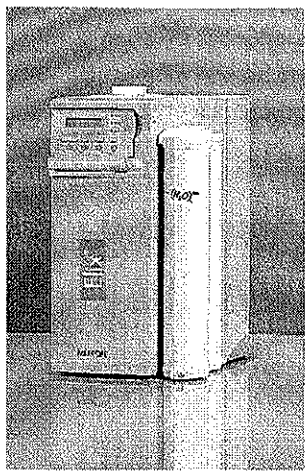
Elix systems are built using the same components as RiOs systems and have therefore identical dimensions.

Elix 3 : 3 L/h (*)
Elix 5 : 5 L/h (*)
Elix 10: 10 L/h (*)

(*) +/- 15 % between 7 and 35 degree centigrade.

Water Quality :

Resistivity	> 5 MΩ.cm
TOC:	< 50 ppb
Bacteria	<1 cfu/ml



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Elix Characteristics

- Optimized Progard Pretreatment Pack
- Water flow rate independent of temperature
- Higher feed water recovery
- Low noise pump
- High / Consistent Quality Water (ions, organic)
- Compact and complete
- Complete control & easy display
- Choice of display language (FR,UK,GE,SP,IT)
- Automatic storage of operating parameters
- Upgradeability to higher flow rates
- Low Operating Costs & Easy Maintenance

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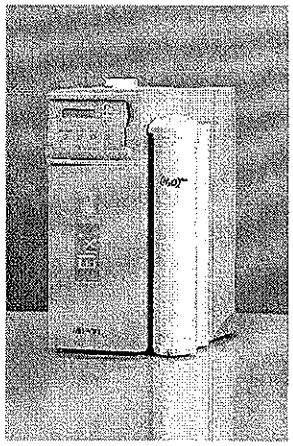
Elix and Still: Comparison





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Electrical Power use: Elix and Still

Product Water	Power
2 LPH	1500 watts
4 LPH	3000 watts
8 LPH	6000 watts
12 LPH	10000 watts
4 LPH 2X still	6000 watts

- Elix power consumption is ~50 watts.
- A still can use 200 times more electricity than Elix

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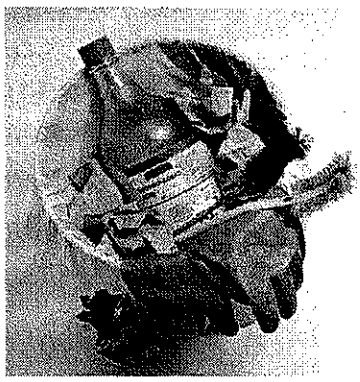
30% reamy vs 4% by distillation.

Maintenance: Elix and Still

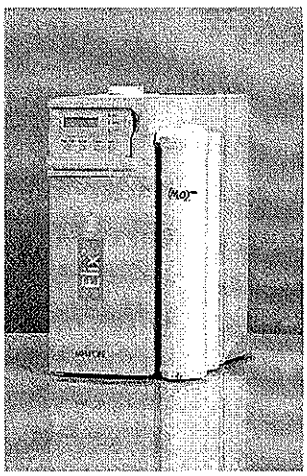
Elix minimum maintenance:
Progard replacement
RO Sanitization

Still maintenance:
Regular cleaning with acid
Risk of breaking parts

Pre-treatment (by DI)
reduces the maintenance
but increase operating costs.

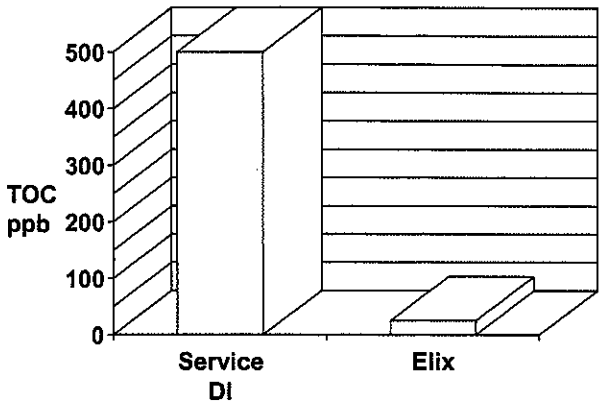


Elix and Service DI :Comparison



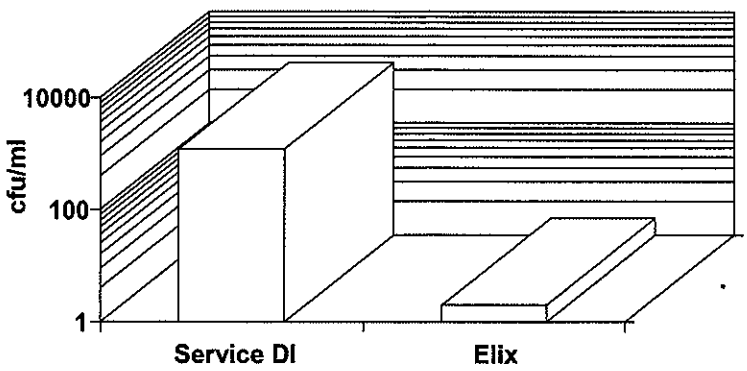


TOC: Elix and SDI



Bedford, MA tap water
2000 ppb TOC, 100 µS/cm
Service DI: 1/4 ft^3, (1) carbon, (2) DI

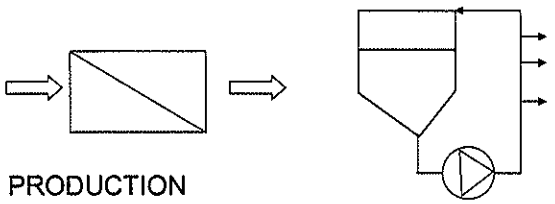
Bacteria: Elix and SDI



Bedford, MA tap water
2000 ppb TOC, 100 µS/cm
Service DI: 1/4 ft^3, (1) carbon, (2) DI

Storage: a practical necessity

Reverse osmosis and Elix systems have a limited instantaneous production.
The choice of the system is generally made on the basis of an 8-20 h running time per day, with water storage allowing a distribution at the required flowrate.



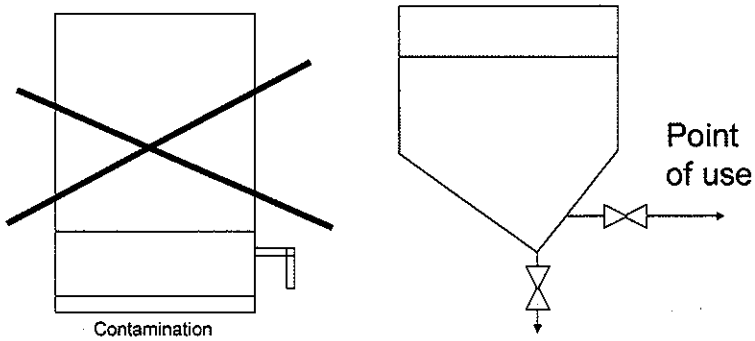
PRODUCTION

Sized according to daily needs

STORAGE + DISTRIBUTION

Sized according to instantaneous requirements

Reservoir for Purified Water



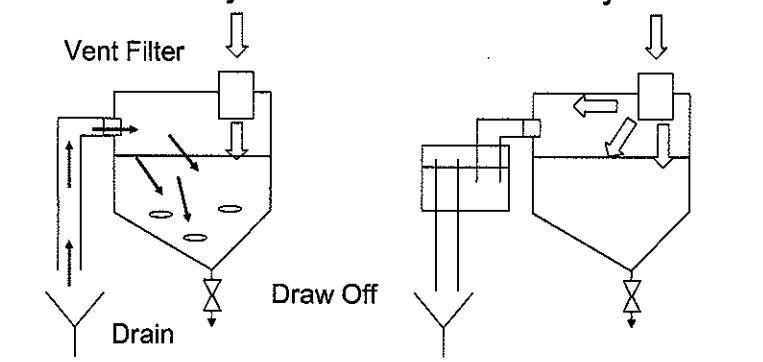
Flat bottomed reservoir

- Incomplete emptying.
- Build up of contaminants.
- Complete rinsing is impossible

Conical bottomed reservoir

- No dead volume.
- Complete rinsing and emptying is impossible

Tanks: Vent Filters and Overflow



During draw off, most of the air come from the drain: contamination

During draw off, all the air is filtered : no contamination

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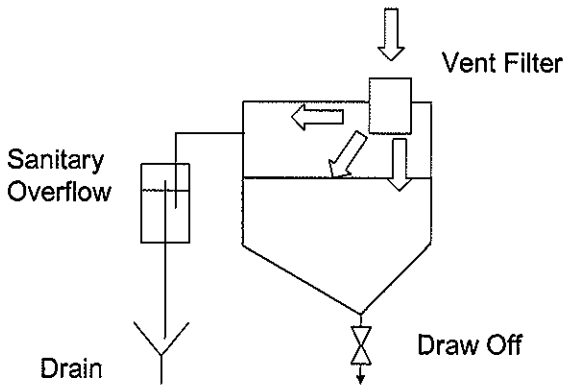
Well protected Reservoir ?



Formation of Biofilm on the inner walls.

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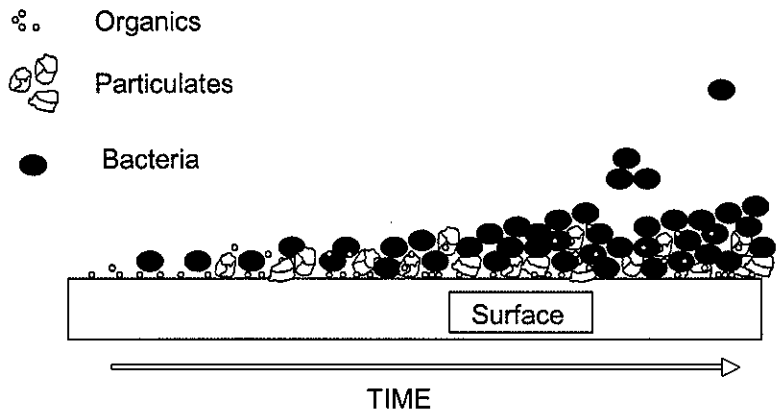
Biofilm development



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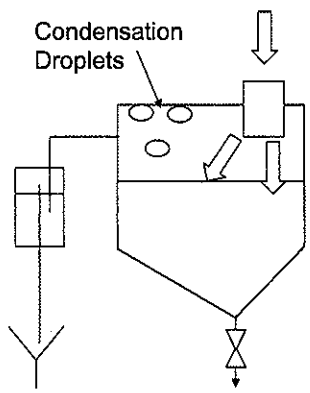
Removal of Biofilm by sanitization ?

Chemical sanitisation (NaOCl, NaOH...etc) :

- Effective on surface in direct contact with water (tank and distribution loop)
- Ineffective on surfaces above the water level (condensation droplets on the roof of the tank)
- Rinsing / decontamination is time consuming



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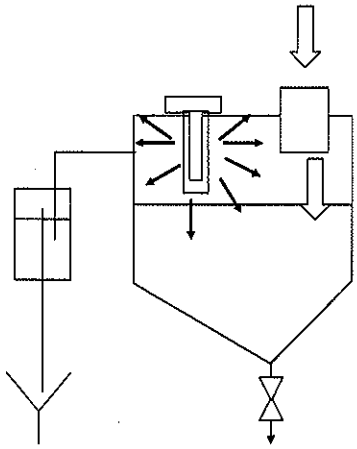
Against Biofilm: UV Lamp inside Tank

UV_{254} for 10-30 min/ day :

Protects the whole interior of the tank from biofilm formation

Has a bactericidal action directly on the stored water



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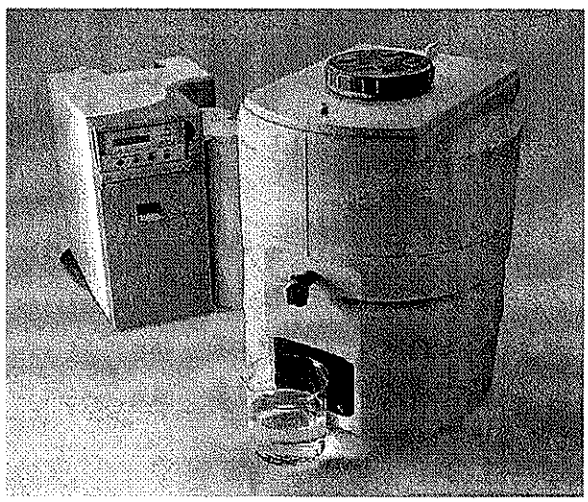
A range of tanks available in all sizes starting from Lab sizes to Large sizes



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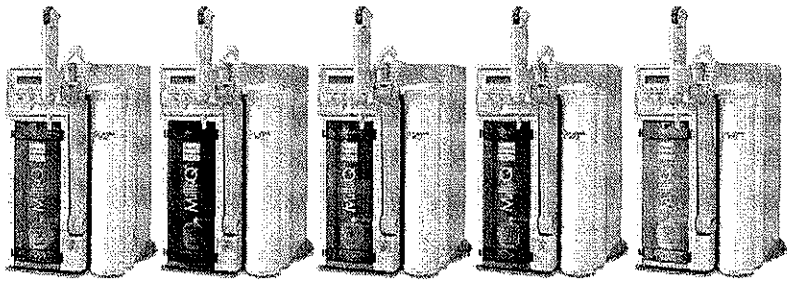
Stainless steel type — not very good resistant to chemical

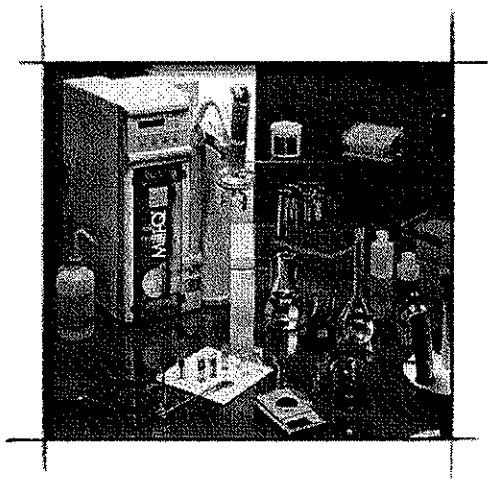
Plastic type — Cheap & resistant to chemical.

Milli-Q Type 1 Water Systems



All these Milli-Q systems produce Type 1 water, but each incorporates different purification technologies and is dedicated to a specific application field.

Milli-Q Academic A10



Milli-Q Academic Applications

- Analytical Chemistry: production of standard solutions, final glassware rinsing water in non critical applications (elemental analysis down to 1 ppb level). Technologies: Spectrophotometry, Spectroscopy, Atomic Absorption, Atomic Emission, ILC,GC
- Organic chemistry: solutions for reaction, pH solutions preparation
- Biochemistry: production of non critical solutions and buffers

Resistivity : > 18.2 MΩ.cm @ 25°C
TOC : 5 to 10 ppb

Milli-Q Gradient A10

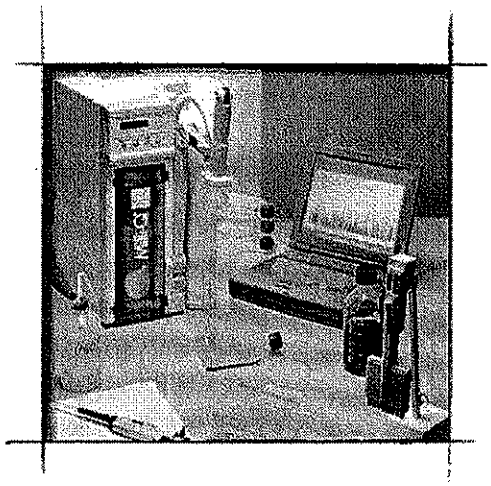


Milli-Q Gradient Applications

- Chromatography: HPLC, LC, LC/MS, GC-MS, GC (Volatile Organic Compounds analysis)
- Dissolution testing
- Langmuir monolayer analysis
- Graphite Furnace Atomic Absorption ILC, Capillary Ion Analysis, (down to 1 ppb)

Resistivity : > 18.2 Megohm.cm @ 25°C
TOC : 0.5 to 5 ppb

Milli-Q Biocel A10

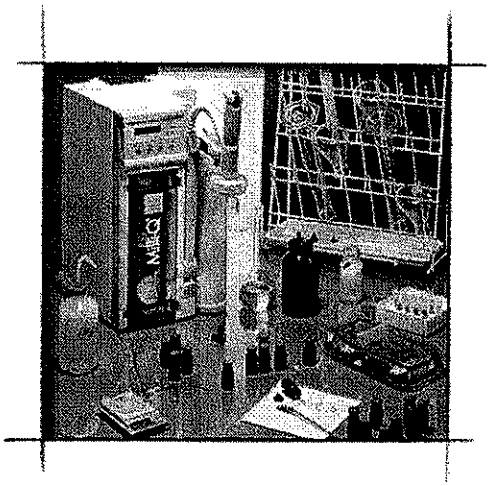


Milli-Q Biocel Applications

- Affinity Chromatography, Protein and Nucleic acid isolation, ELISA tests
- Electrophoresis gels and buffers preparation, Capillary Electrophoresis
- Preparation of media for microbiological, plant and mammalian cell culture

Resistivity : > 18.2 Megohm.cm @ 25°C
TOC : 5 to 10 ppb
Pyrogens: < 0.001 EU/ml

Milli-Q Synthesis A10



Milli-Q Synthesis Applications

- Defined Culture Media preparation for mammalian (including human) cell culture
- Preparation of buffers for 2 D Electrophoresis and blotting (Nothern, Southern, Western)
- Preparation of solutions for PCR and DNA Sequencing

Resistivity : > 18.2 Megohm.cm @ 25°C
TOC : 1 to 5 ppb
Pyrogens: < 0.001 EU/ml

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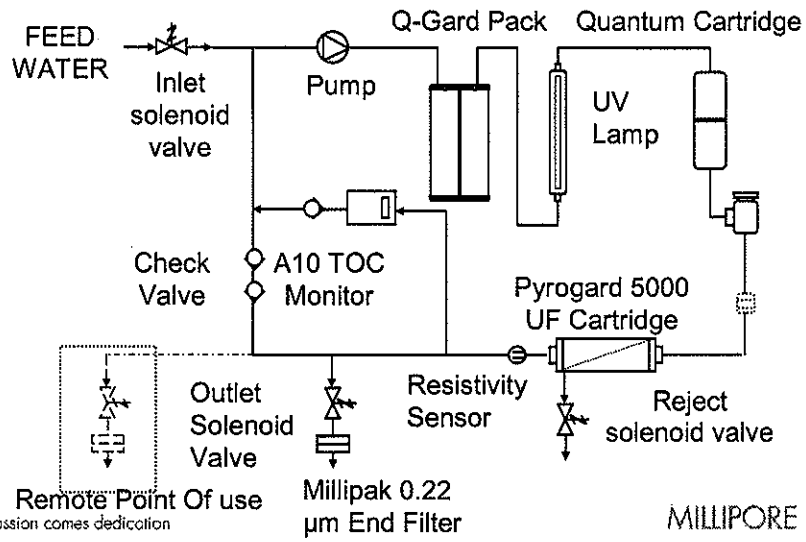
Milli-Q Synthesis A10



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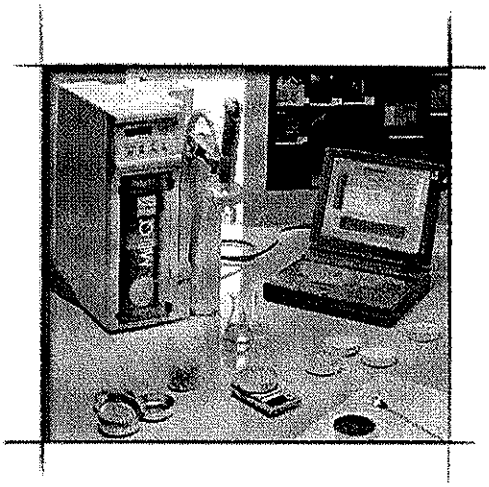
To prevent contamination

Milli-Q Element



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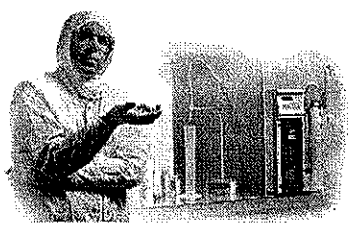
Milli-Q Element Applications

Low level elemental analysis (down to the ppt level and below by techniques such as ICP-MS, ICP-OES, GFAA,ILC). For memory : ratio on a time scale

1 ppm	(1 mg/L)	1 second in 11.5 days
1 ppb	(1 µg/L)	1 second in 32 years
1 ppt	(1 ng/L)	1 second in 317 centuries

mg → 10^{-6}
ng → 10^{-9}



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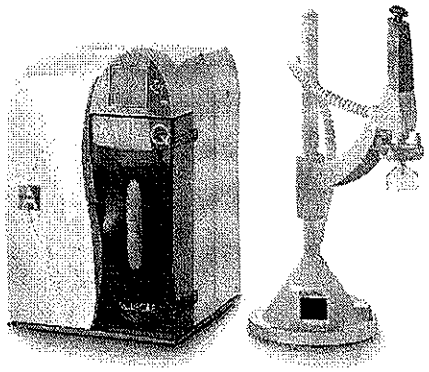
Milli-Q Advantage A10



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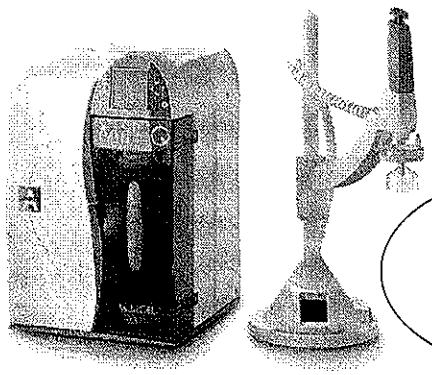
Milli-Q Advantage
Delivering more than expected



New Water Purification Strategy

With passion comes dedication

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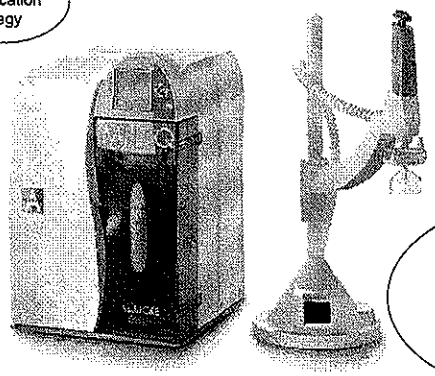
Milli-Q Advantage

New Water Purification Strategy



New Water Delivery Concept

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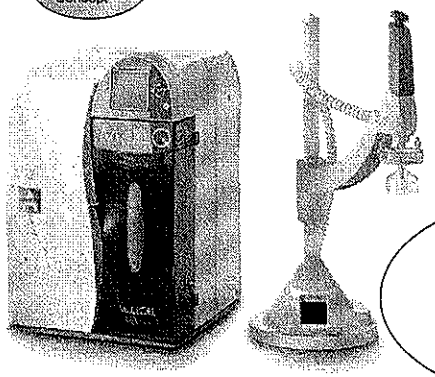
Milli-Q Advantage

New Water Purification Strategy

New Water Delivery Concept



Information adapted to user needs

With passion comes dedication

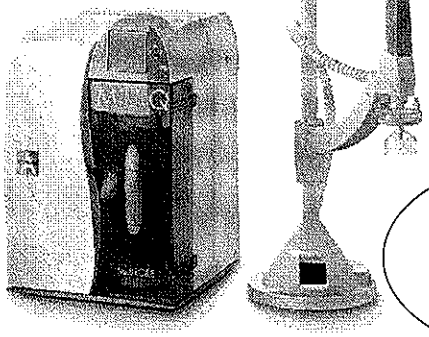
MILLIPORE

Milli-Q Advantage

New Water Delivery Concept

Information adapted to user needs

New Water Purification Strategy



Total Quality Insurance

With passion comes dedication

MILLIPORE

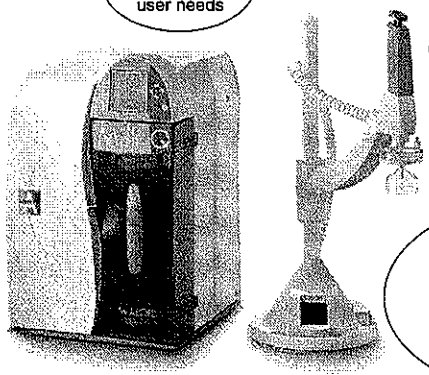
Milli-Q Advantage

New Water Delivery Concept

Information adapted to user needs

Total Quality Insurance

New Water Purification Strategy



User Friendly Operation

With passion comes dedication

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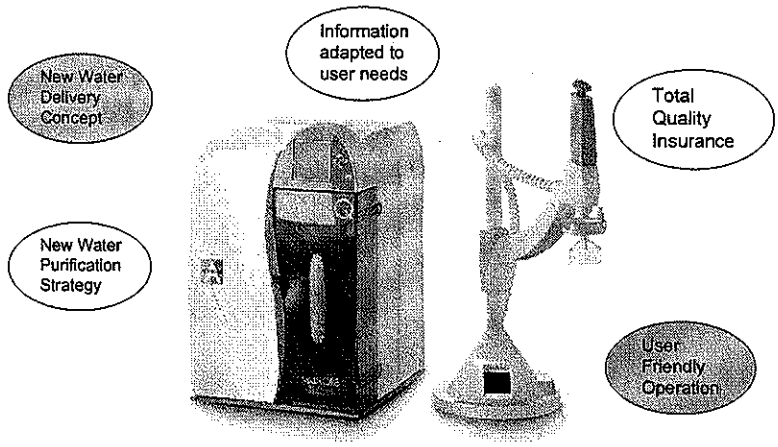
Milli-Q Advantage



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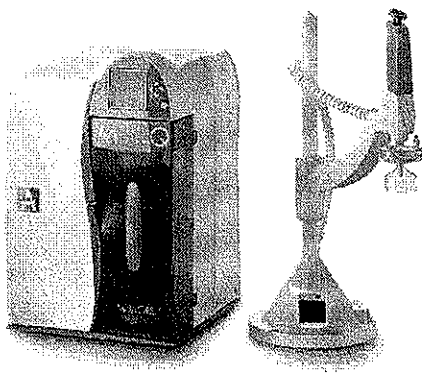
1 - New Water Purification Strategy



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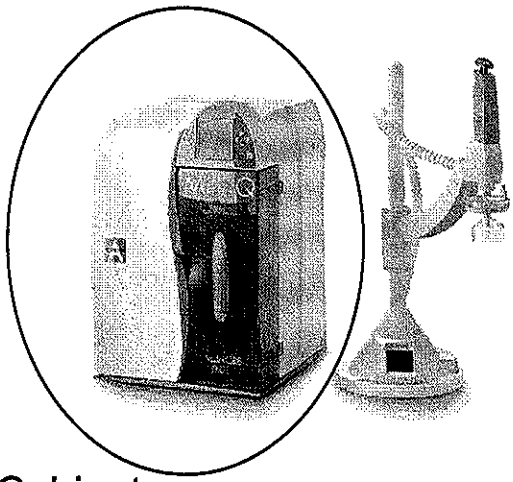
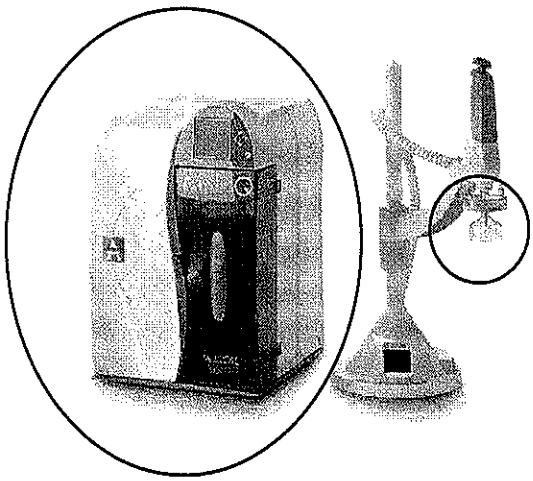
New Water Purification Strategy



Cabinet

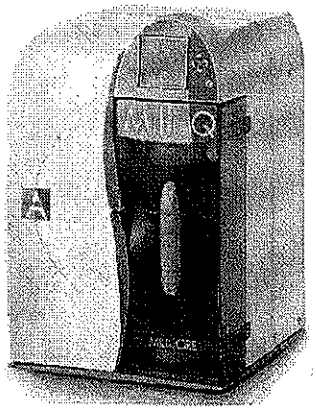
New Water Purification Strategy



Q-Pod™
Polisher

uv lamp

Milli-Q Advantage Cabinet



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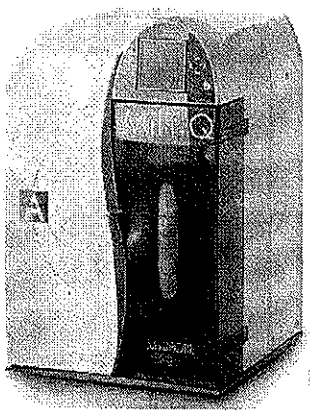
Milli-Q Advantage Cabinet

Pure Water



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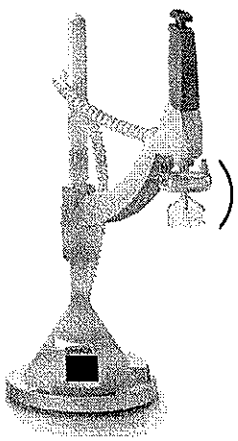
Milli-Q Advantage Cabinet

Pure Water



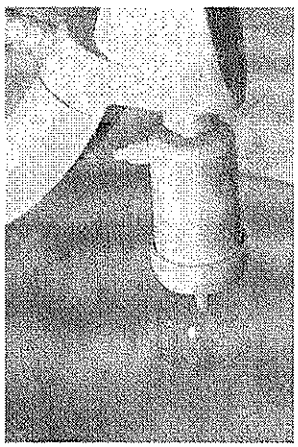
18.2 MΩ.cm
TOC < 5 ppb

Q-Pod Polishers



The most critical purification step for the user application comes last

Example

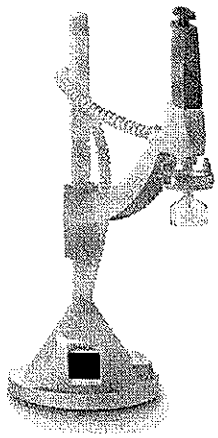


For pyrogen or Rnase sensitive applications, the new validated Biopak ultrafiltration cartridge

Benefits of this new strategy

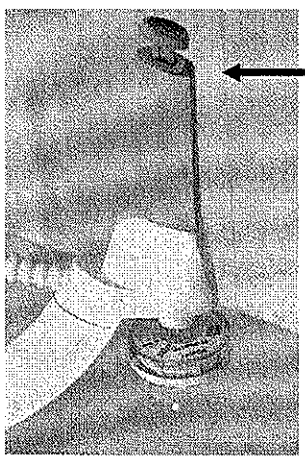
- Better Water Quality
  - Water better adapted to the specific user needs
  - Polisher family to match several applications
- Versatility:
  - Change easily the final water quality to match the application – no need to buy a new system
  - Different water qualities available from different Q-Pod
- Easier maintenance: consumable replacement only (no more sanitization)

2 - New Water Delivery Concept: Q-Pod



- Variable flow rate: from drop by drop up to 2L/min
- Water dispenser easy to move
- Volumetric dispensing
  - Easy to perform
  - Adapted to glassware height and shape

Flow Rate : from **drop by drop** up to **2L/min**



No Flow

Low Flow

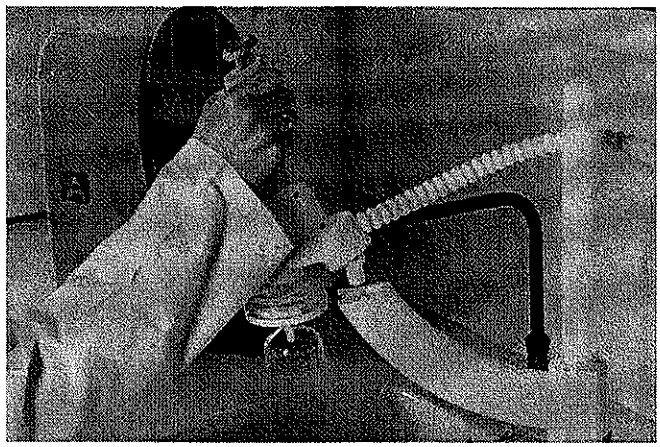
Mid Flow

High Flow

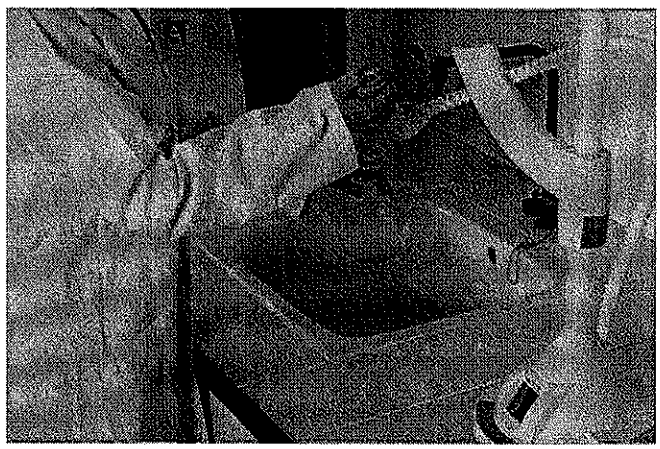
High Flow locked

Maximum time defined in the set point section accessible only to the system manager

Q-Pod: removable dispenser

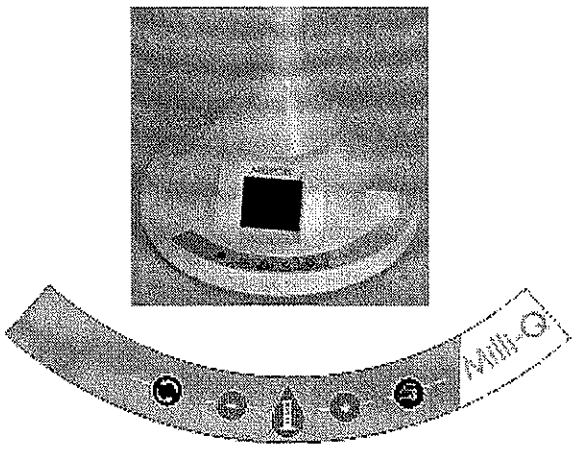


Q-Pod: easy move of the dispenser



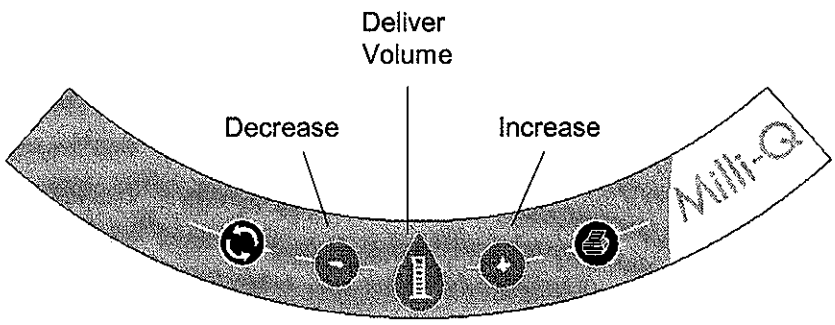
Tubing Length = 80 cm – Recirculation to outlet valve

Volumetric Dispensing: from the Q-Pod basis

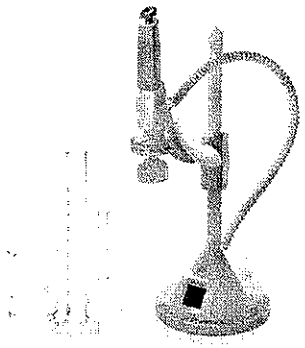


Easy selection and delivery of volume

Volumetric Water Delivery



Easy Volumetric Water Dispense



- Height of Q-Pod mast adapted to glassware height
- Arm position variable
  - Up and down
  - Left & right
- Water delivery easily programmed from the Q-Pod basis

3 - Information adapted to user needs



User: just wants good water, easily

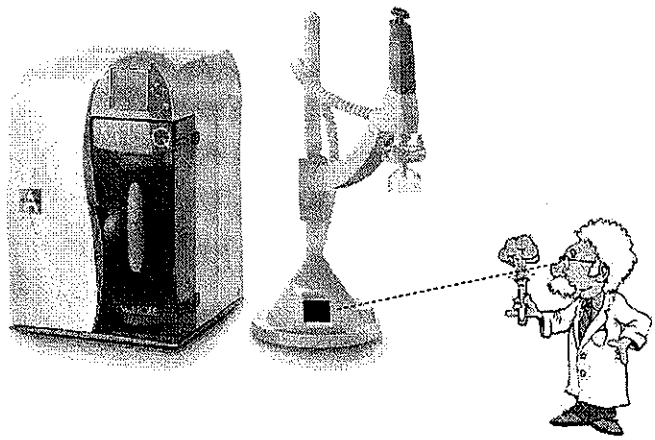


Maintenance:
takes care of the system



Lab Manager: wants to control the critical parameters

Basic User Interacts only with Q-Pod



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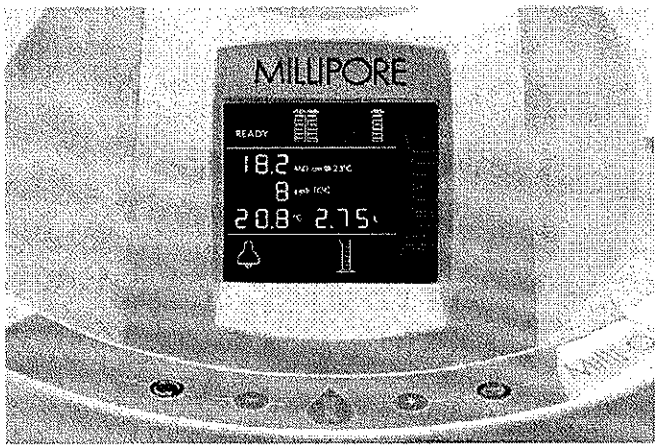
.... Easy to read



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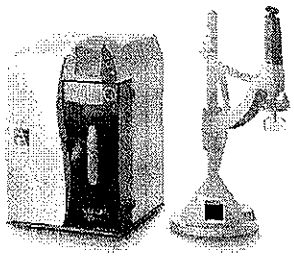
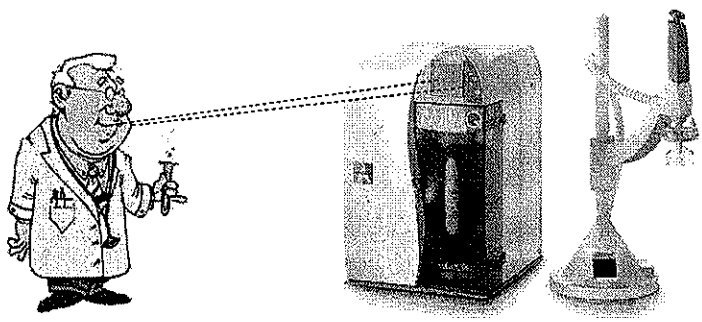
Alerts, Maintenance & Alarms





Are a concern for the maintenance Person

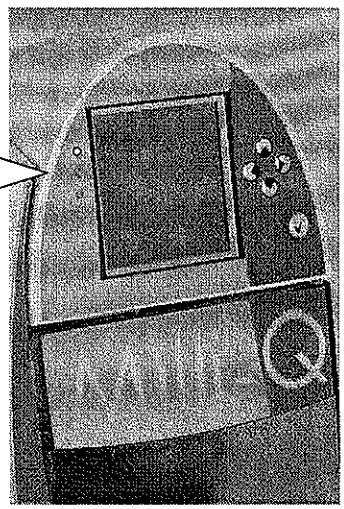
Who interacts with the main display & keypad



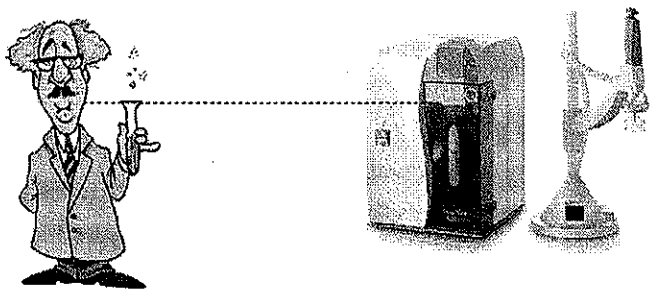
The Main Display has 3 areas

Traffic light Operation Summary

- ○ OK
- ○ Maintenance
- ○ Alarm

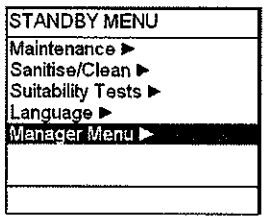


The lab manager interacts with main display…

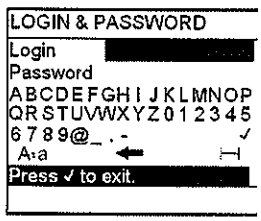


...and has access to a protected area

The Manager Menu where he can change critical data



Protected by identification code and password



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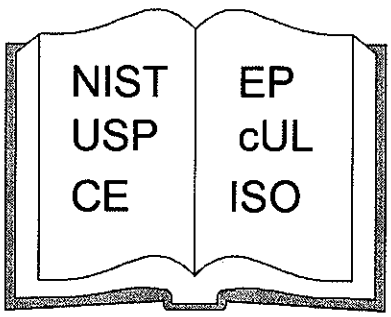
4 – Total Quality Insurance

- Our customers are asking for more and more Quality Insurance and norms



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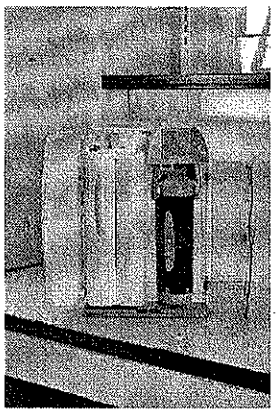
4 – Milli-Q Advantage :Total Quality Insurance

- Milli-Q Advantage comes with all the Quality Insurance these demanding customers may ask for
- Some examples:
  - Resistivity calibration according to International Standard
  - Consumables with tag
  - Certificates of calibration for resistivity and TOC monitoring

New Resistivity Calibration Method

- Milli-Q Advantage systems is calibrated according to a procedure developed by Millipore with an Internationally recognized Institute. This means:
  - A full traceability of the calibration to an internationally recognized, national standard based on a primary cell
  - A calibration performed by the most accurate method available today to calibrate measuring instrument in low conductivity ranges.
- Benefits
  - Unique peace of mind for the end user
  - Locking spec for Millipore

Consumables e-Sure Technology



RFID

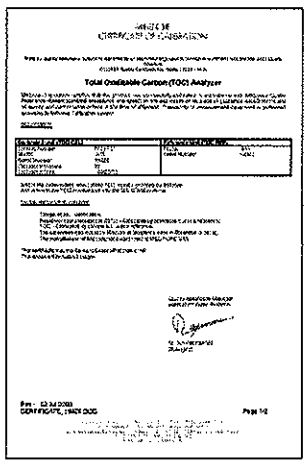
Radio
Frequency
Identification
Detection

Allows to identify the consumable installed.

CONTENT
RESERVED
TEST KEY
'MADE BY MILLIPORE'
NAME
PACK TYPE
CATALOG NUMBER
LOT NUMBER
SERIAL NUMBER
INITIAL CAPACITY 1 (liters)
INITIAL CAPACITY 2 (liters)
VOLUME USED 1
VOLUME USED 2
CARTRIDGE EXHAUSTED FLAG 1
CARTRIDGE EXHAUSTED FLAG 2
INSTALL DATE
INSTALL MONTH
INSTALL YEAR
MANUFACTURING DATE
MANUFACTURING MONTH
MANUFACTURING YEAR

Certificates of calibration

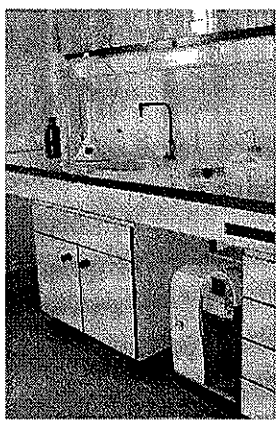
- Certificate of calibration for
  - Resistivity Meter
  - TOC meters



5 - Convenience

- Convenience is built in the system's design to delight our customers and our service engineers
- Convenience means:
  - Easy water delivery
  - Easy access to information
  - Easy installation
  - Easy maintenance
  - Easy service

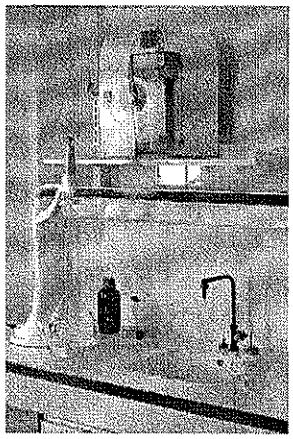
Main Unit Bench Integrated



This new design allows to better integrate the Milli-Q Advantage in the laboratory design.

The production unit can be installed under the bench …

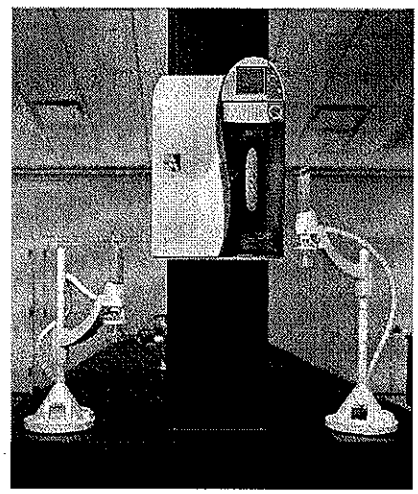
Main Unit High on a wall



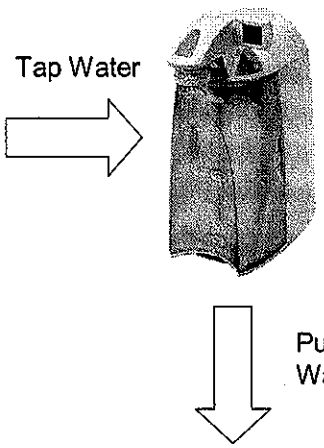
... or high on a wall.

As a result, only the Q-Pod occupies space on the bench, making Milli-Q Advantage the lab water system with the smallest footprint in the world.

Up to 3 Q-Pod connected to a Milli-Q

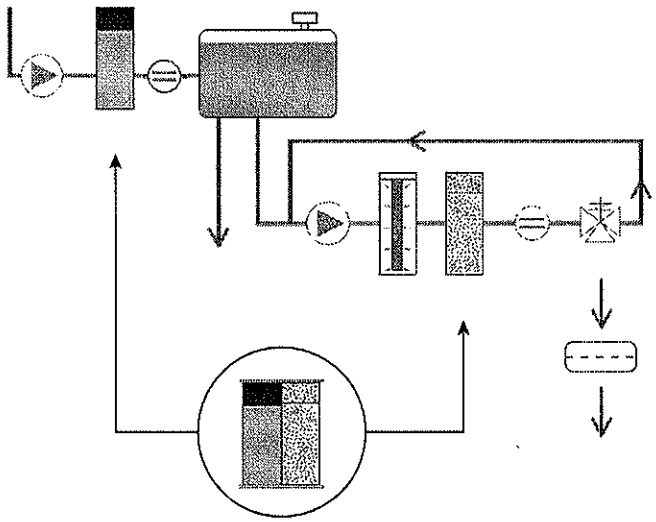


Also Ultrapure from Tap
Direct-Q 3 two in one concept



- Ultrapure Water
- Directly from tap water
- Delivered the way the user wants it
- Easy Installation
- Easy Operation
- Easy Maintenance
- For peace-of-mind
- Economy (2 different types of lab water)

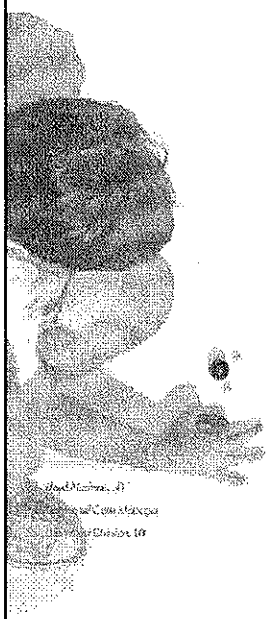
How it works: Direct-Q 3 Flow Schematic



Easy Maintenance: consumables exchange



- Limited to consumable replacement when prompted by system
  - SmartPak
  - Millipak
  - UV lamp (2 years)
- Patented self lock mechanism makes replacement easy
- No sanitization procedure



Larger Flow Production Units
Elix and RiOs

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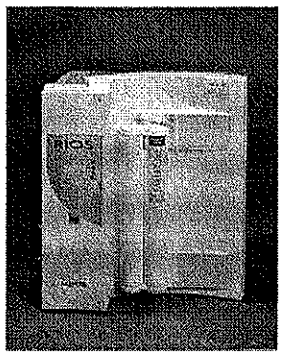
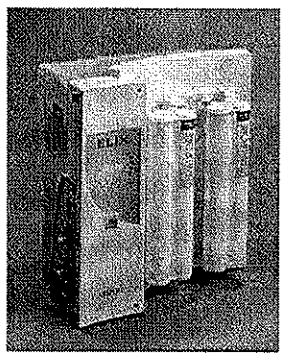
Millipore Systems Designed to Answer Customers Requests

- Water must be of consistent quality
  - The system integrates a complete purification sequence that insures to reach the water quality desired





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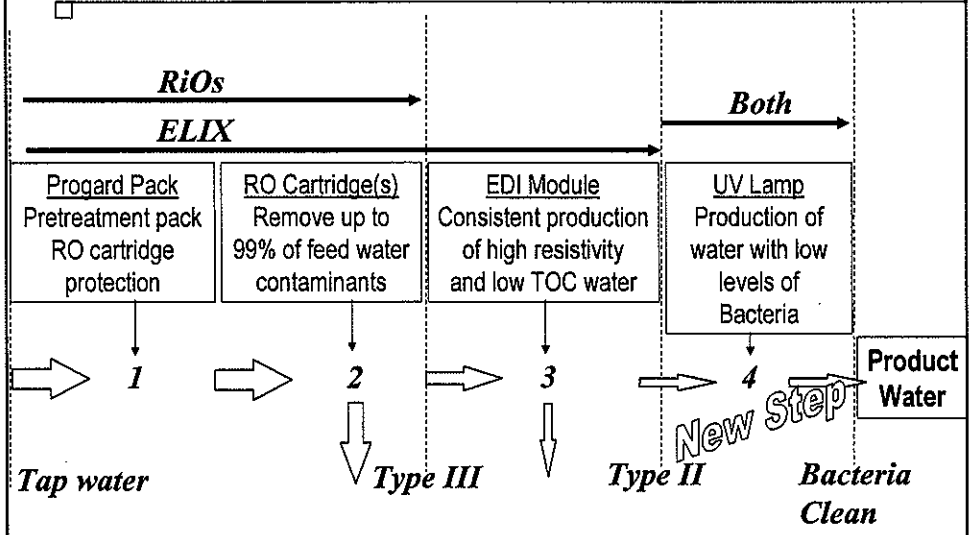
The purification sequence in the Type III and Type II water systems : RiOs and Elix



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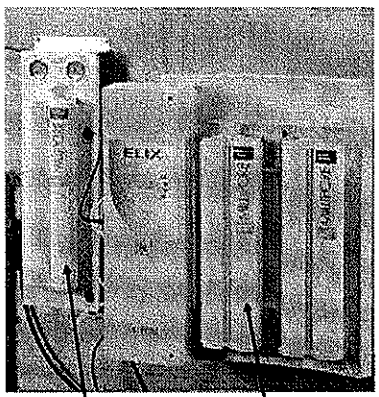
Simplified Pretreatment and Pak Options

- ProGard TL System Paks
  - (2) Options to cover range of feedwater
- Prepak L, pre-system pak
  - Higher chlorine and fouling levels
- Need for back-washable sand and carbon filters minimized
  - Needed for larger systems when fouling and/or chlorine levels are high
- Softener: Not required by New Elix module



Prepak L
(with wall bracket)

Progard TL

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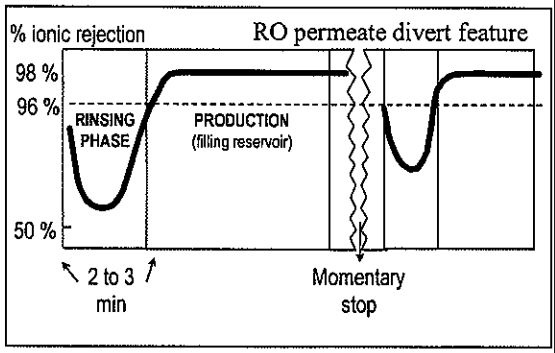
Automatic Maintenance Functions

- Automatic RO membrane flush
- RO permeate diverted to drain at start-up
  - Poor quality water discarded
  - Warms UV lamp
- Choice of automatic RO membrane cleaning cycles
  - Sanitization (Cl_2)
  - ROClean A and B

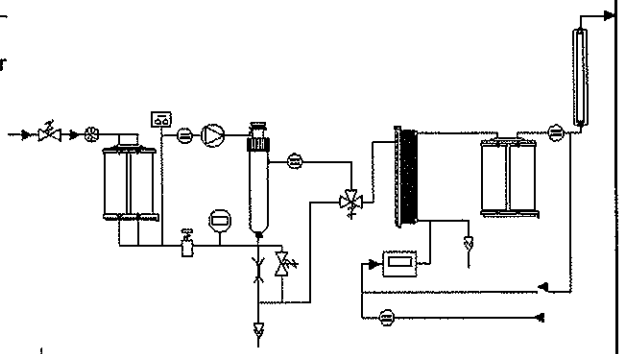


Millipore Systems Designed to Answer Customers Requests

- The systems should be designed to help working in GxPs environment
  - Explicit messages and Maintenance and Alarm LED's-signals indicate with no possible confusion the operator what to do
  - Extensive Qualification Package available
  - Good design practices respected
  - The monitoring of the water quality is possible after each purification step.
    - Feed Conductivity, permeate conductivity for Elix & RiOs, product resistivity and TOC for Elix & Milli-Q are measured

Complete Control over Water Purity

- (2) Conductivity cells
  - Feed and RO product water
- (2) Resistivity cells
  - RiOs, *(option)*
    - Polisher
    - Distribution Loop
  - Elix:
    - Elix module or Polisher
    - Distribution loop, *(option)*
- TOC monitoring, *(Elix option)*
  - Elix module, polisher, or distribution loop
- USP Suitability Test:
  - Resistivity and TOC designed to pass USP suitability tests



With passion comes dedication

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Millipore Systems Designed to Comply with International Standards

- Water quality monitors, TOC and Resistivity meters, are designed to
  - Undergo the USP suitability test
  - Undergo simple controls of calibration in the field
  - or be re-calibrated.

With passion comes dedication

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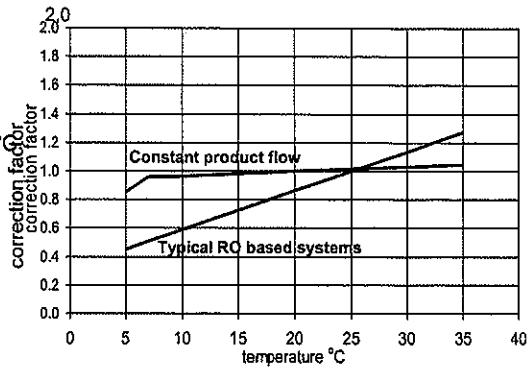
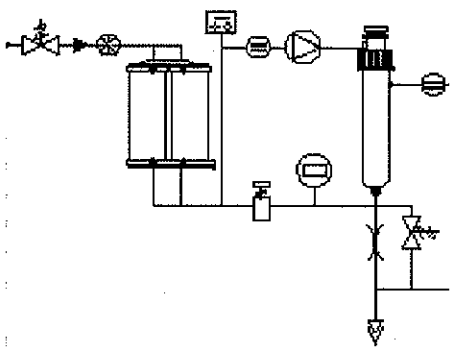
Constant Product Flow Rate

- Constant product flow rate regardless of temperature
  - Constant flow between 7 and 35 °C
  - Typical RO based systems
    - 3% decline per every one °C
    - As high as 50% decline



RO High Recovery Loop

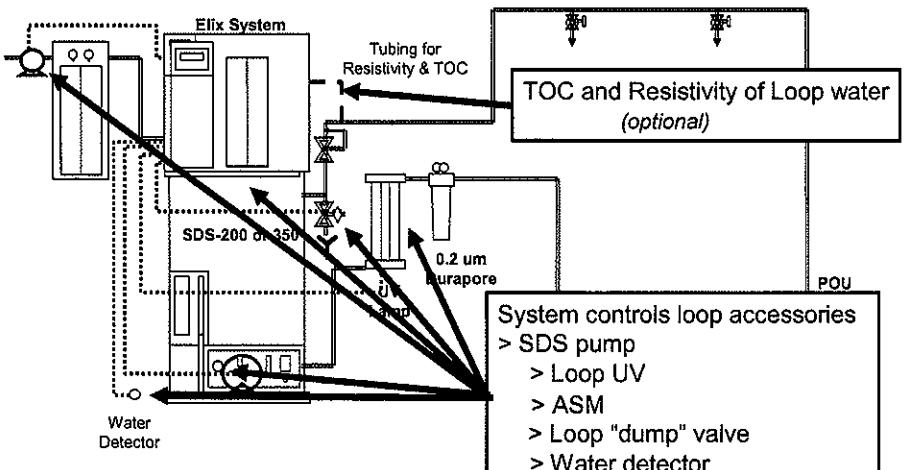
- **A portion of the RO reject water is recycled back to the RO feed**
  - Adjustable it is possible to control reject flow rate to drain depending on the feed water quality
- **Recovery rates up to twice as high as typical RO-based systems**
  - RiOs systems up to 70%
  - Elix up to 50%

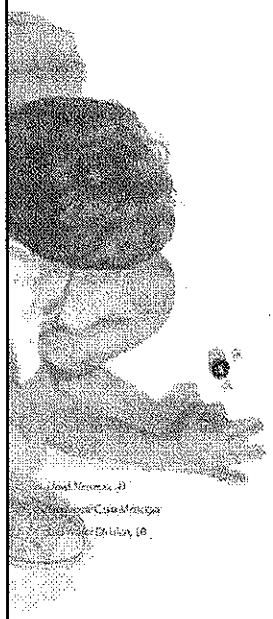


Millipore Elix Designed to Meet Customers Requests

- In conventional Installs, the system is nice and user friendly, but the accessories (pretreatment and control box) aren't
  - Additional Pretreatment similar to the standard pretreatment
    - Easy to use Plug and Use Pack concept
  - Full Control of Dedicated Accessories from the Elix Unit
    - Loop dump valve option controlled by Elix Water system
    - Water Detector option built in, (linked to inlet solenoid valve outside the system)
    - ASM Automatic Sanitization Module
    - Distribution Pump for the distribution loop
    - In line U.V. lamp for the distribution loop
    - Booster pump option controlled by system for low feed pressures

A real breakthrough
The system is not only the heart but also the brain





Total Water Solutions

With passion comes dedication

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More than Systems, a Complete Solution

- The systematic delivery of the adequate quantity and quality of pure and ultra-pure water is key to the laboratory operation
- Depending on the needs (quantity, quality and regulations), the architecture of the laboratory and other factors, the best solution can differ dramatically from one customer to the next
- Very often, the right response to the need is a water purification and delivery concept rather than simply a water production unit

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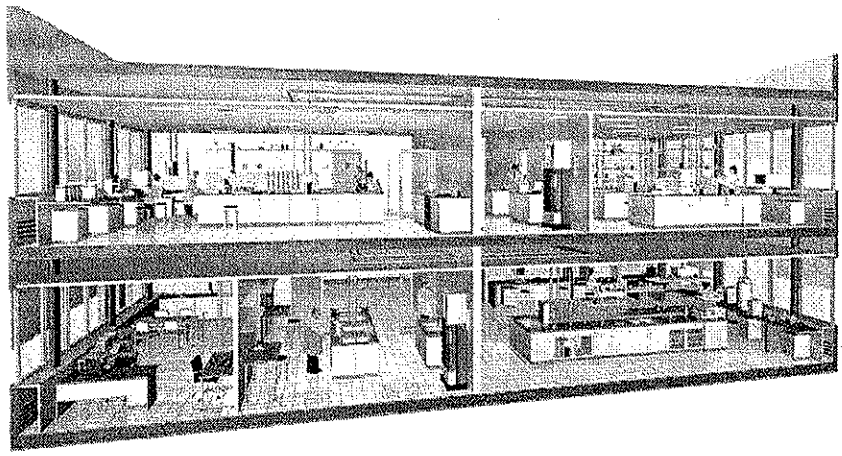
Pure water is required in every lab



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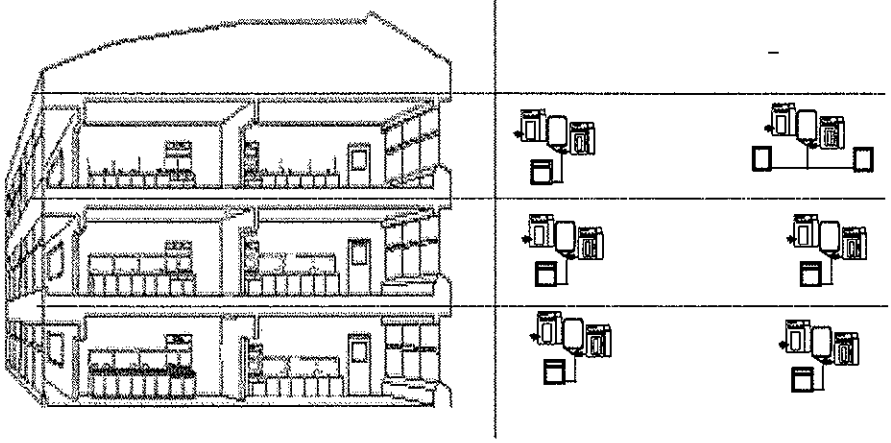
One common solution to feed a building



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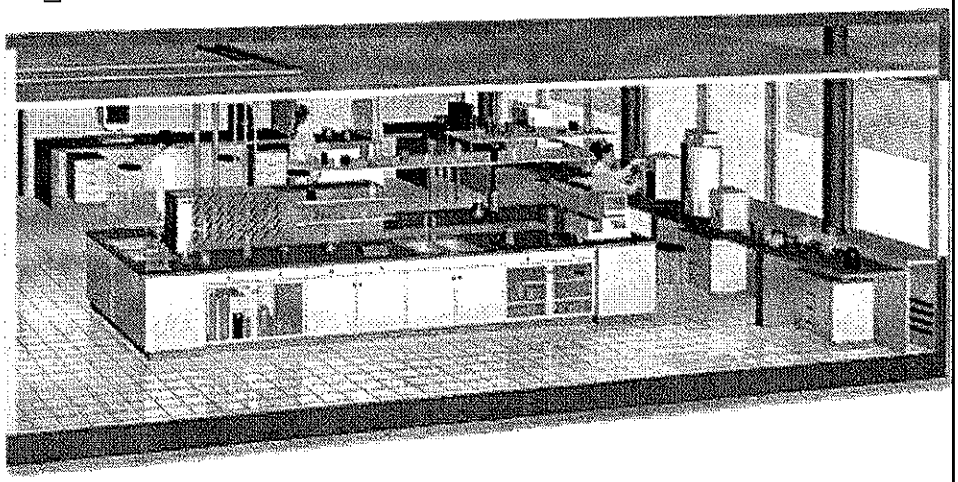
From the market's first bench-integrated ultrapure water systems…



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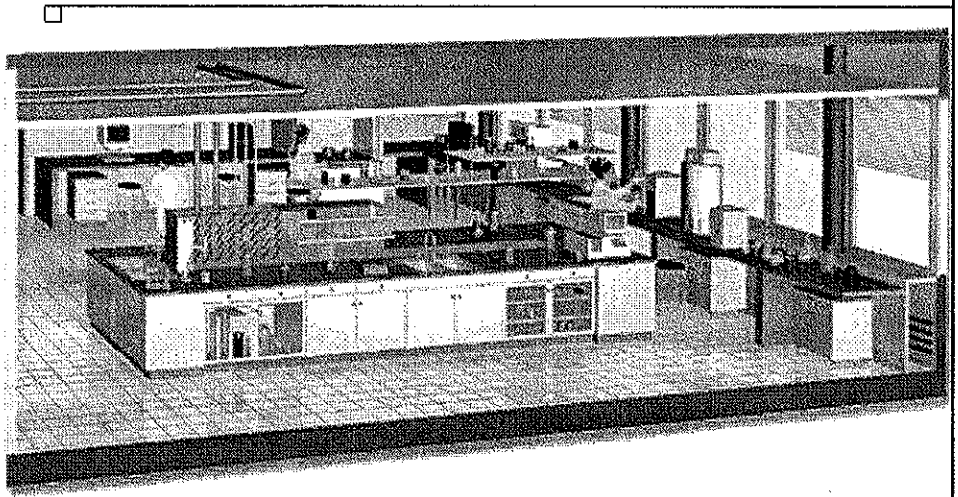
To complete Water Purification Chains…



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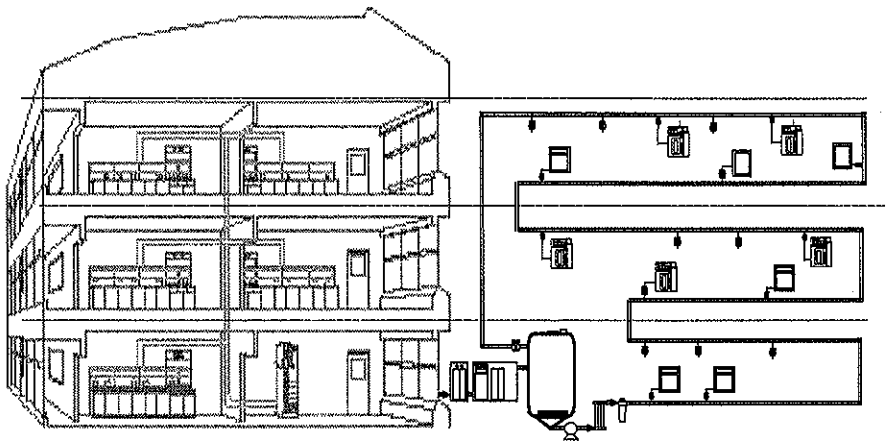
Another possible common solution



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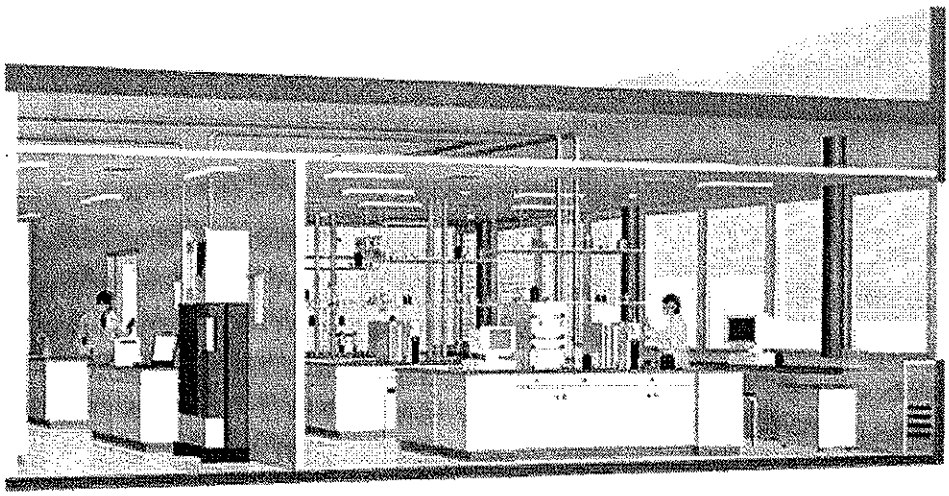
To the recently introduced, state-of-the-art, "boutique central sytems"



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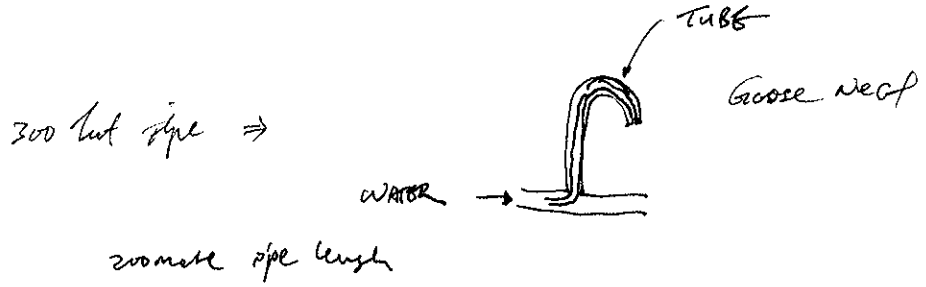
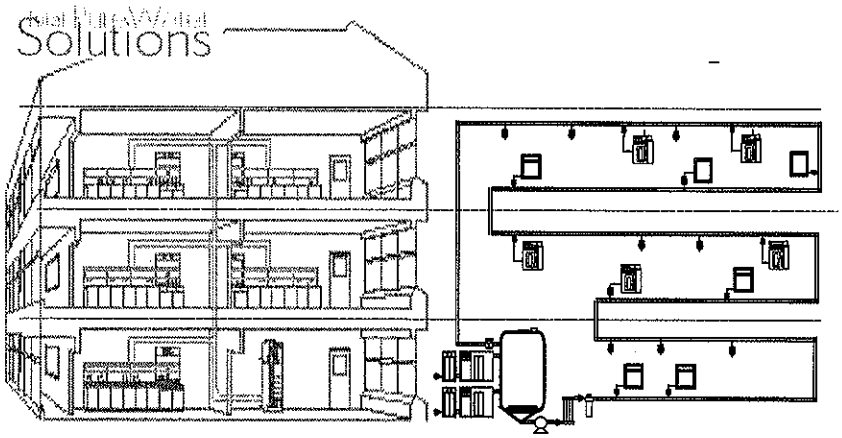


Alternatives are often very interesting to consider : Duplex solutions



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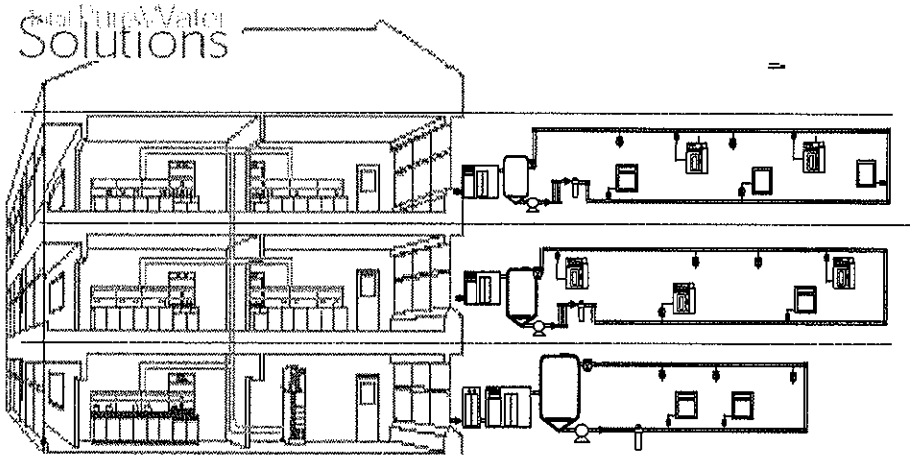
eg with 2 pumps. is not a good idea.

Alternatives are often very interesting to consider : Floor by floor solutions



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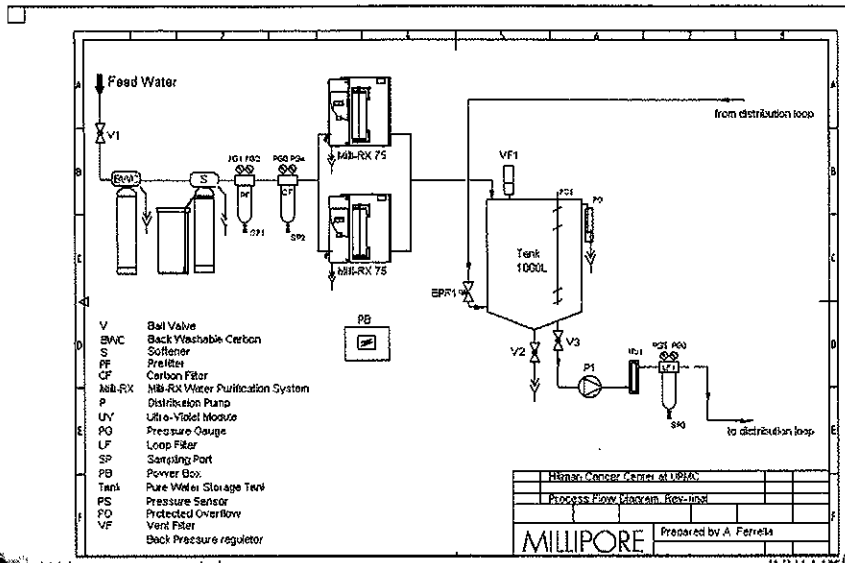
Total Water Purification System
Example; Hillman Cancer Center at UPMC
Academic and Medical Research at the University of Pittsburgh



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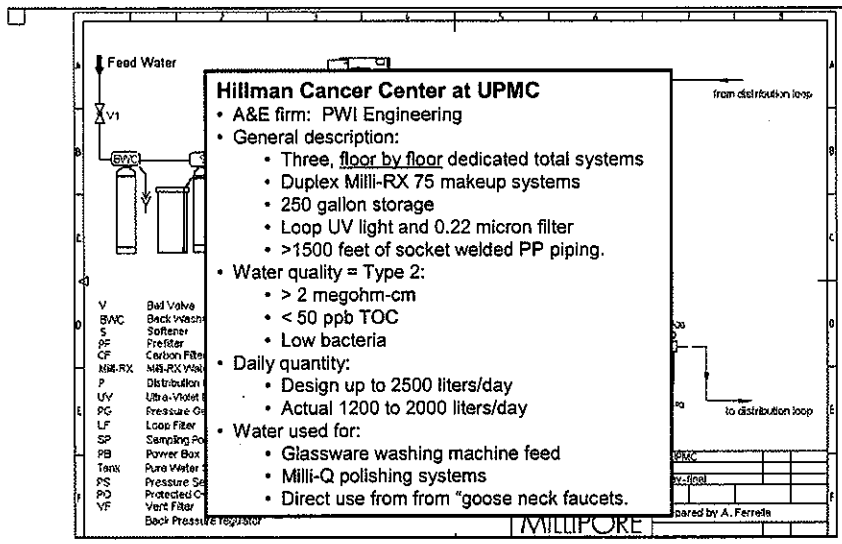

Hillman Cancer Center at UPMC

- A&E firm: PWI Engineering
- General description:
  - Three, floor by floor dedicated total systems
  - Duplex Milli-RX 75 makeup systems
  - 250 gallon storage
  - Loop UV light and 0.22 micron filter
  - >1500 feet of socket welded PP piping.
- Water quality = Type 2:
  - > 2 megohm-cm
  - < 50 ppb TOC
  - Low bacteria
- Daily quantity:
  - Design up to 2500 liters/day
  - Actual 1200 to 2000 liters/day
- Water used for:
  - Glassware washing machine feed
  - Milli-Q polishing systems
  - Direct use from from "goose neck faucets.

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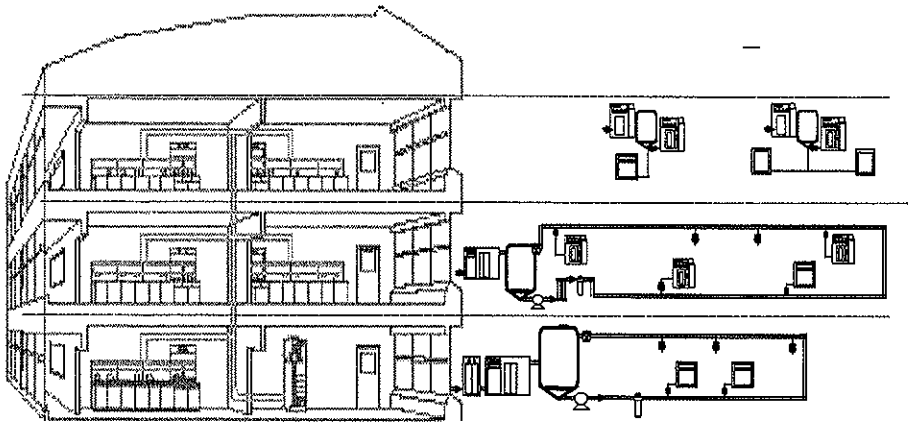
Alternatives are often very interesting to consider, a mix



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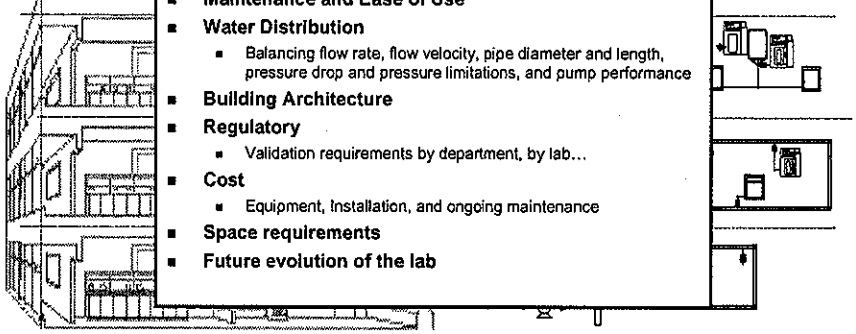
A thorough analysis of all relevant parameters is needed to define the best approach

- **Water Quality and Quantity**
  - By department, by laboratory and by individual use point
- **Control over performance**
  - Reliability and Consistency to each use point
- **Maintenance and Ease of Use**
- **Water Distribution**
  - Balancing flow rate, flow velocity, pipe diameter and length, pressure drop and pressure limitations, and pump performance
- **Building Architecture**
- **Regulatory**
  - Validation requirements by department, by lab…
- **Cost**
  - Equipment, Installation, and ongoing maintenance
- **Space requirements**
- **Future evolution of the lab**



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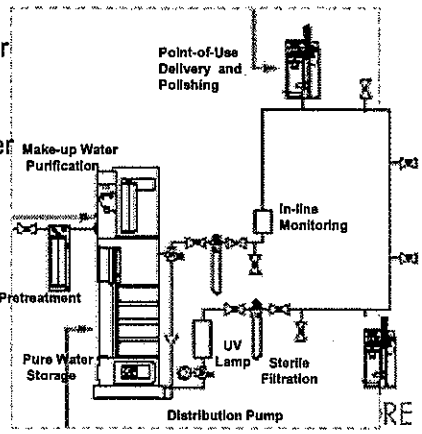
Each step must be considered

- Once the needs of each department and the specific water requirements of each laboratory and individual use point are understood it is possible to determine the total water system design for a laboratory facility.
- If a central location or a floor-by-floor solution is considered as the best approach, each part must be taken into account to ensure the right water quality at each Point of Use
  - Make-up water system
  - Storage
  - Distribution loop
  - Accessories
  - Point of Use Polishers



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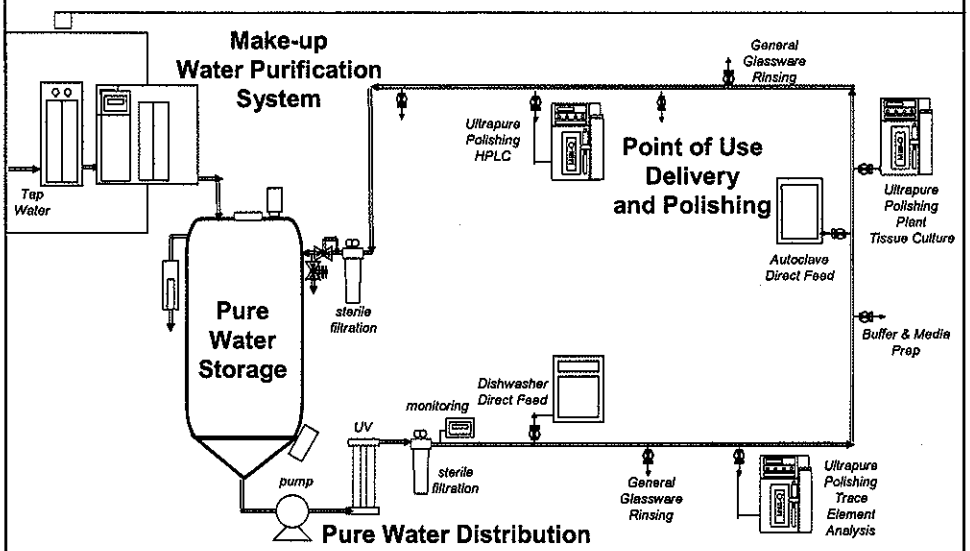
Example of Custom Total Water Purification Solution



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Illustration; not to scale

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Design Rules

- Make up water system
  - Purification technologies involved to reached the desired level of quality
  - Purification sequence adequate for best results
  - Monitoring of the water quality (after each purification step…)
  - Control / Alarms for operating conditions
  - Design for field calibration
  - Design for easy qualification

Design Rules

- Tank Design requirements
  - 100% drainable
  - Opaque
  - Minimize angles
  - Smooth surface
  - Turn-over of the water in the tank
  - Over-flow sanitary and disconnected from the drain
  - Vent filters should prevent contamination of the pure water by air-born contaminants
    - Bacteria
    - But also volatile organics and CO_2

- PPTF more expensive than stainless steel.
- PP pipe with welding. - Best in term of price
- PVC & ABS - Not so good / suitable
-

Design Rules

- Sizing the couple: Make-up water system & the tank
  - RO-based water system should work more than 10 hrs per day
  - Tank capacity should be close to 1 day of production
- Selection of materials in contact with water at all levels (purification, storage and distribution)
  - Regulations to abide by and certification needed for qualification if applicable
  - Chemical compatibility with sanitant
  - Level of quality desired

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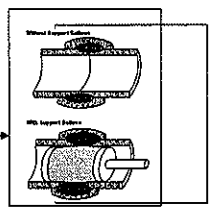
Design rules

- Distribution loop
  - Material
  - Accessories included in the loop
  - Welding technique to use (electro-fusion…)
  - Connections
  - On line and in line Monitoring devices
    - TOC-meters
    - Conductivity/resistivity-meters
    - solutions for bacteria analysis…
  - Pressure drop evaluation (calculation)
  - Linear velocity in the piping to respect
  - Flow-rate delivered to have sufficient water
  - Definition of the pipe diameter definition based on pressure drop, flowrate and velocity requirements (calculation tables)
  - No dead leg design (6D rule from CFR 212)



IR TECHNIQUE

6D is 6 time the diameter.

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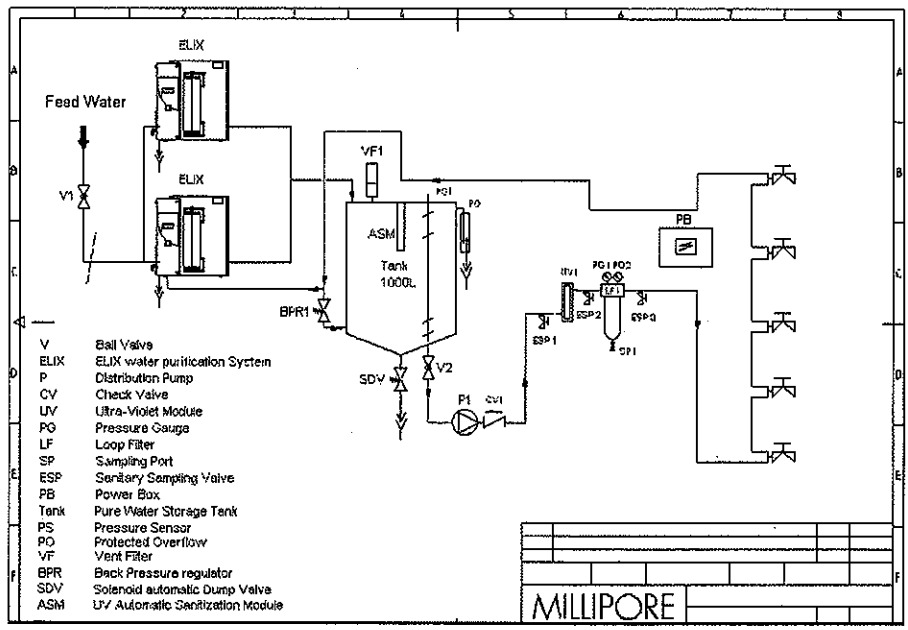
To maintain turbulence flow to prevent bacteria from growing inside the pipe.
∴ sufficient speed but less pressure drop

Example of design for typical application 1

- Production of Purified Water according to EP and USP in an environment where water availability is critical.
  QC laboratory or laboratory Building in a Pharmaceutical plant
  - Elix make up water system (duplex or simplex depends on the criticality of the water availability)
  - Storage tank — for one day's capacity
  - One distribution pump + one spare — for availability of the water 24/7
  - UV module on the loop — for bacteria control
  - ASM UV in the tank — for bacteria control
  - Automatic dump valve — for periodic flushing and producing fresh water during periods of low use
  - Loop filter with 0.22µm Durapore® — for bacteria removal
  - Millipore ESP sanitary sampling port — for reliable and easy microbiological analysis
  - Monitoring of the loop water quality — for good control of the water quality Resistivity and TOC



Example of design for typical application 2

- Configuration recommended by Millipore for production of pure water for washing machine in non stringent environment but in which water availability is critical
  General Hospital for example
  - Elix or RiOs make up water system (duplex)
  - Duplex pump — for no water shortage
  - Storage tank — for one day's capacity
  - ASM UV in the tank — for bacteria control
  - Automatic dump valve — for periodic flushing and producing fresh water during periods of low use
  - Monitoring of the loop water quality — for good control of the water quality Resistivity and TOC (ELIX only)

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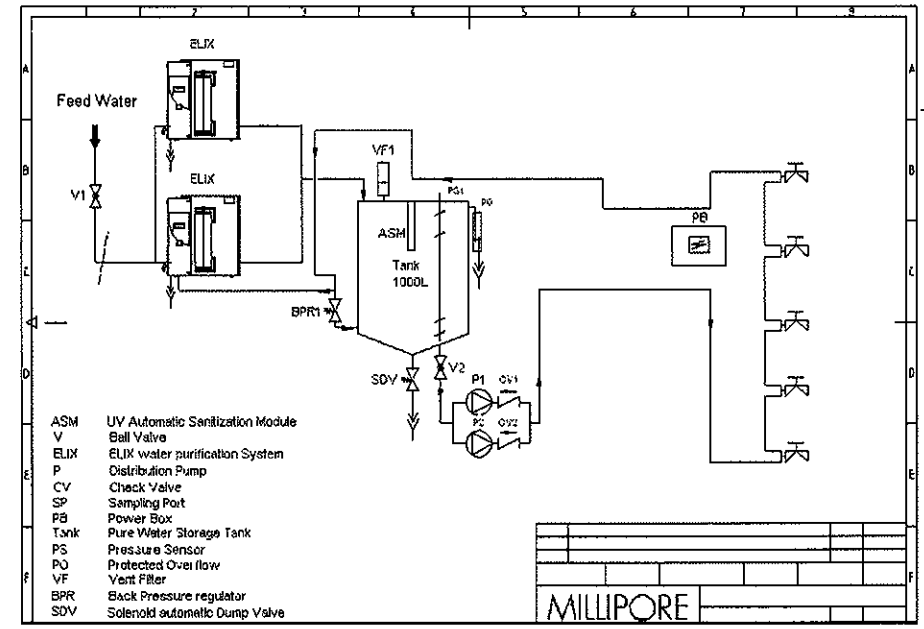

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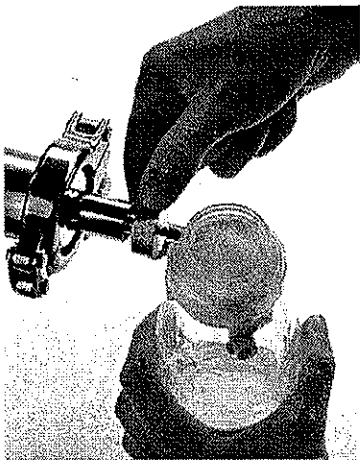
The Millipore Water Solution also includes MicropreSure for Bacteriological Analysis





0.35 µm membrane

Millipore Can Provide a Complete Support

- This support is present at all the project steps
  - The definition of the needs
  - The design of a total solution
  - The estimation of the budget
  - The delivery of the units, accessories and consumables
  - The installation
  - The users training
  - The preventive maintenance
  - The full support for validation

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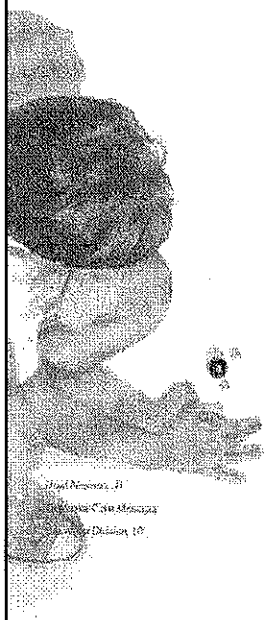

Validation

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- Current guidelines for Pharmaceutical Water Purification Systems
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- Millipore Systems Qualification Product

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- Large Service Products

What is a regulatory agency?

- For most of all the areas where risks for safety exist, governments of all the country created regulatory agencies.
- Their daily mission consists
  - to define and provide rules to follow
  - to be sure of the respect of the rules through inspections for example
  - to punish in case of deviation.

Pharmaceutical regulatory agencies

- Pharmaceutical area which is directly linked to public health is governed by powerful regulatory agencies.
  - For the U.S. market: Food and Drug Administration
  - For the European market: European Agency for the Evaluation of Medicinal Products
  - For U.K.: UK Medicines Control Agency
  - For Japan: National Institutes of Health Sciences
  - ...

Regulatory agencies guidelines

- In their role of providing guidelines the pharmaceutical regulatory agencies publish GMP (Good Manufacturing Practices).
  - e.g.: FDA GMP, European GMP, Orange Guide (UK)

What is GMP?

- GMP (Good Manufacturing Practices) is a quality management system which describe the organization and the conditions for the preparation of the finished product.
- GLP (Good Laboratory Practices): created for the labs where the finshed products are data. Concept of GLP used by a lot of labs not only in pharmaceutical area (environmental, ...).
- Objectives of these standards
  - Ensure the Quality, Safety, Efficency of the final product

Differences between ISO and GMP

- ISO is a voluntary standard. Participants are required to document the operations that they perform and to perform the operations as documented.
- GMP/GLP are mandatory regulations. People operating in specific fields have to apply those rules. The rules not only indicate that the operations should be documented, but also give guidelines on which operations should be performed and how they should be performed.

GMP Reminder

- Why is it necessary to follow GMP ?
  - To ensure a minimum level of quality, safety, and efficiency in the manufacturing of the pharmaceutical product
  - To sell pharmaceutical products
    - The sales of some product (drug in particular) is allowed after strict verification of the compliance to the standards by the regulatory agencies. The consequences in case of deviation can be economically dramatics

GMP content

- Contents of this standard (inspections)/ CFR 21 Parts 210 and 211
  - General Provisions
  - Organization and Personel
  - Building and Facilities
  - **Equipment (Conception, Validation, Calibration, Maintenance)**
  - Control of Components and Drug Product Containers and Closures
  - Production and Process Controls
  - Packaging and Labeling Control
  - Holding and Distribution
  - Laboratory Controls
  - Records and Reports
  - Returned and Salvaged Drug Products

Validation & Qualification

- What is Validation?
  - -USP-NF 26-:

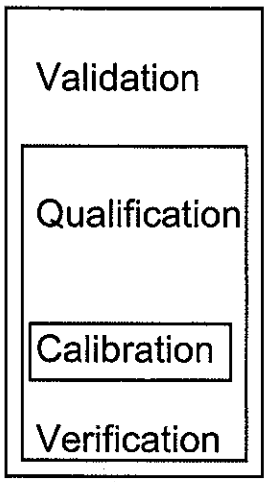
    "Validation is the procedure whereby substantiation to a high level of assurance that a specific process will consistently produce a product conforming to an established set of quality attributes is acquired and documented"

- What is Qualification?
  - Qualification are the different steps of the Validation of an equipment.

Equipment Qualification

- An instrument operating in a validated laboratory should ideally operate within specifications 100% of the time,provide automatically documented evidence of this fact and warn the operator if performance is outside of specifications.
- Equipment Qualification generates documented evidence that ensures with a high degree of certainty that a Laboratory Equipment performs consistently within pre-determined specifications

Validation, Qualification, Calibration,Verification



Validation: verification and documentation that a process (for instance an analytical procedure in a laboratory) is in agreement with the expectation (accuracy, precision in a specific detection range)
Qualification: verification and documentation that an instrument (for instance an HPLC system or a water purification system) behaves as specified. Qualification is a part of validation.
Calibration: verification and documentation of the specific functions of an instrument (for instance a resistivity monitor). Calibration is a part of qualification.
Verification: a calibration substitute

Validation

- What is concerned by validation?
  - EU GMP directive 91/356/EEC and 91/412/EEC
  - *"Premises and equipment intended to be used for manufacturing operations which are critical for the quality of the products shall be subjected to appropriate qualification."*
  - World Health Organization good manufacturing practices:
    "The guide on GMP for pharmaceutical products requires validation of critical processes as well as changes in the manufacturing process which may affect product quality." ... ***"A prudent manufacturer would therefore normally validate all production processes and supporting activities, including cleaning operations".***

Validation

- Who is concerned by validation?
  - Pharmaceutical Manufacturing departments and Pharmaceutical QC labs must follow GMP.
  - More the activity/department is close to manufacturing and/or QC and more the obligation is important.
  - Since one year now we observed more and more qualifications in R&D department due to economical reasons and by a move of the inspections on downstream activities.

Validation

- Why is it necessary to validate? (from development to production)
  - To ensure quality, safety efficiency and to decrease the risks of processing problems by a deep understanding of the complete process
  - To sell products by demonstrating compliance with regulatory guidelines
  - To save money by decreasing the risks of regulatory non-compliance and because a fully validated process may require less in-process control and end-product testing
  - To save money by loosing less time in case of any deviation

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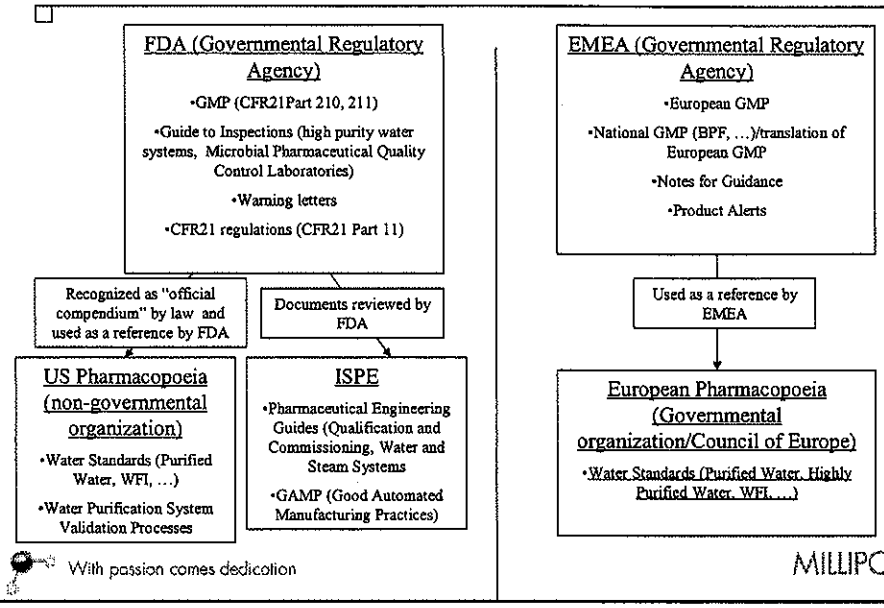
Guidelines for pharmaceutical water systems

- Due to the fact that GMP can not be an exhaustive list of guidelines and or be specific to purified water, most of requirements are based on:
  - GMP main principles (safety, ...)
  - Common and well established good practices
  - Comments during inspections
  - Recognized Standards defined by recognized organizations (U.S. Pharmacopoeia vs FDA, ISPE Baseline vs FDA for pharmaceutical water systems, European Pharmacopoeia vs EMEA, ...).

Many differences in the user requirements may exist due to differences in user references and text interpretation.

What are the links between each organizations



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Water Purification System Validation

- According to the "reference" documents, Validation Process for water purification system is broken down into stages (qualification) described in the Validation Master Plan (VMP)

  - Design Qualification (DQ)

  Definition of the need (User Requirements Specifications), selection of the materials, ...

  - Installation Qualification (IQ)

  "Establishing a high degree of confidence that the equipment as installed is consistent with manufacturers' requirements and specifications"

Water Purification System Validation

  - Operational Qualification (OQ)

  "Establishing a high degree of confidence that the equipment as installed is able to consistently operate within established limits and tolerances"

  - Performance Qualification (PQ)

  "Establishing a high degree of confidence, with appropriate testing that the equipment, under normal operating conditions, will consistently produce a quality product"

Design Qualification

- ***"Establishing standards for quality attributes and operating parameters"*** ***USP26***

  ↳ Define water qualities needed according to:
  - User Requirements Specifications (applications, ...)
  - Cost effective considerations
  - **Regulations: Standard definitions and "Validation/GMP requirements"**

Design Qualification

- ***"Define clear Design"*** **USP26**

  ↳ answering to regulation requirements (Good Engineering Practices)

  ⇒ Water quality compliant with standard specifications is not enough for a pharmaceutical water purification system

  ⇒ Water Purification Installation must answer to Good Engineering Design (no dead legs, ...)

  ⇒ Good Engineering Practices requirements will depend of user interpretation and experience, risk analysis, ...

Responsibilities

- It is the responsibility of the user:
  - to define which water quality he will need for his applications.
    - We can help and advise him according to our knowledge and our experience.
  - to make and to assume his choice (design, material, ...)
    - He is the only one who really know his applications, who can perform a risk analysis, ...
- It is the responsibility of Millipore to give him all the information required to perform the risk analysis, to propose the water purification system able to produce the water quality required, designed and supported according to his requirements.

Design Qualification

- ***"Define clear Design"*** **USP26**

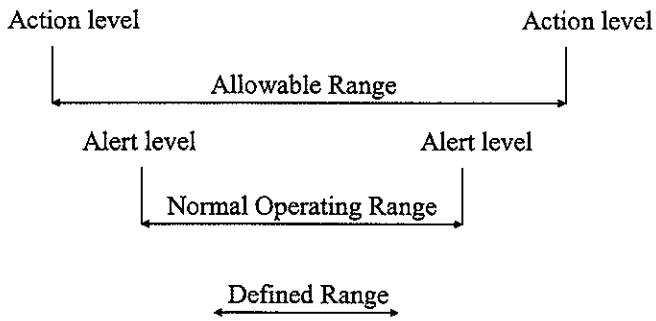
  ↳ according to the water uses

  Deionised water R with a resistivity of not less than 0.18 Mohm.m. **(EUROPEAN PHARMACOPEIA 4th EDITION 2002** Reagents Water for chromatography. **1095503. (7732-18-5)**

  ↳ according to the volume need
  - Max Instantaneous need
  - Total need/day /week /year

Design Qualification

- ***"Define Normal Operating and Allowable Range by defining Alert and Action levels on all the parameters"*** **USP26**



Design Qualification

- ***"Define systems and subsystems suitable to produce the desired quality attributes from the available source water"*** **USP26**
  - Selection of the technologies to use for the
    - Pretreatment (filters, softener, RO, EDI, ...)
    - Storage and Distribution
    - Final treatment (Desionization, microfiltration, ...)

"Selecting equipment, controls, and monitoring technologies" **USP26**

- TOC, conductivity need to be followed for Purified Water
- Microbiology contamination need to be followed for Purified Water

Installation Qualification

- ***"Consisting of instrument calibrations inspections to verify that the drawings accurately depict the as-built configuration of the water system and, where necessary special tests to verify that the installation meets the design requirements"*** **USP26**
  - **Conformity with P&IDs (Piping and Instrumentation Diagrams), PO and contracts, ...**
  - **Identification and verification of the documents (calibration certificates, owner's manual, material in contact with water list,...)**
  - **Verification of the compliance of the installation according to the manufacturer's specifications**
  - **...**

Systems Overview and Installation Qualification Content

- Overview
  - Good Testing Practices Description
    - Qualification process,
    - Requalification Guidelines
    - Form Completion requirements
    - Water Purification System drawing
    - Commissioning Report/PO compliance
    - Qualification Protocol Approval
- Installation Qualification
  - Administrative/Descriptive Part
    - System Description and Specifications
    - Qualifier and System Identification
    - Certificates of conformity + calibration
    - Installation Site Requirements
    - Material in contact with water list
    - Ancillary Equipment
  - Tests
    - IQ Verification Procedures (Fluid & Electrical connections, Consumable installation)

Operational Qualification

- ***"Consisting of tests and inspections to verify that the equipment, system alerts, and controls are operating reliably and that appropriate alert action levels are established"*** **USP26**
  - **Verification of the monitoring functions**
  - **Verification of the electronics functions (alarms, ...)**
  - **Verification of the hydraulic functions**

Systems Operational Qualification Content

- Operational Qualification
  - Introduction
  - Qualifier & System Identification
  - Test Devices Information
  - Displayed Control & Quality Readings
  - Electronic Functions Verification of the whole equipment (hearth + additional equipment)
  - Hydraulic Functions Verification (hearth + additional equipment)
  - Monitoring Functions Verification (hearth + additional equipment)

Performance Qualification

- ***"Development of prospective PQ stage to confirm the appropriateness of critical process parameter operating ranges"*** **USP26**

  "Verification of alert and actions levels for key quality attributes and operating parameters" **USP26**

Systems Performance Qualification Content

- Performance Qualification
  - Introduction
  - Qualifier & System Identification
  - Performance Qualification Forms Examples

Maintenance Procedures

- ***"Validation Maintenance Program (also called continuous life cycle) that includes a mechanism to control changes to the water system and establishes and carries out scheduled preventive maintenance including recalibration of instruments"*** **USP26**

  "Validation Maintenance includes a monitoring program for critical process parameters and a corrective action program" **USP26**

Systems Maintenance Procedures Content

- Maintenance Procedures
  - Introduction
  - Qualifier & System Identification
  - Recommended Annual Maintenance Procedures Description
  - Documentation of regular (annual) maintenance procedures completed for the different units of the water purification system
  - On-going log of periodic maintenance carried out by the user / service engineer

Requalification

- ***"Requalification Program Schedule for periodic review of the system performance and requalification"*** **USP26**

- ***"Revalidation may be divided into two broad categories:***
  - *revalidation after any change having a bearing on product quality.*
  - *Periodic revalidation carried out at scheduled intervals."*

"It is well known that process changes may occur gradually even if experienced operators work correctly according to established methods. Similarly, equipment wear may also cause gradual changes. Consequently, revalidation at scheduled times is advisable even if no changes have been deliberately made." **World Health Organization Essential Drugs and Medicines Policy Who good manufacturing practices: main principles for pharmaceutical products**

Complete Validation Steps

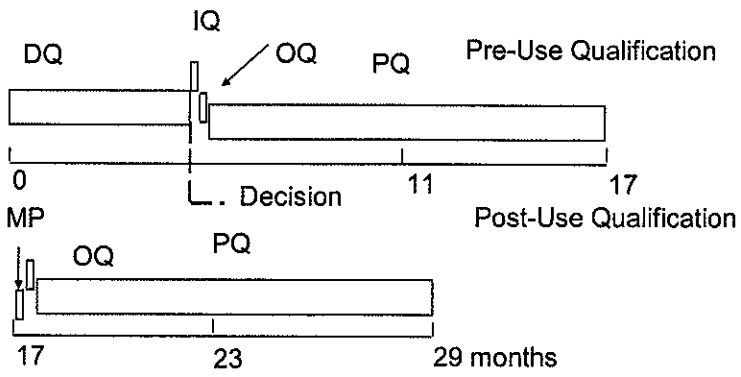


Table of Content

- Pharmaceutical regulatory environment
- Current guidelines for Pharmaceutical Water Purification Systems
- Validation of a pharmaceutical water purification systems/Millipore Program
- Systems developed according to regulatory requirements
- Millipore Large Systems Qualification Product
- Large Service Product

Water Purification System characteristics for GMP environment

- Monitoring

  ISPE Baseline Water and Steam Systems Key Concepts

  "In regards to chemical purity, the quality attributes themselves (properties of water produced), may be monitored at or after each process step, and the proper operation confirmed directly."

  ⇒ Operation continuously monitored by sensors (°C,Bar, µS/cm…)
  ⇒ Purified Water quality monitored regularly (µS/cm, MΩ.cm,°C,TOC)
  ⇒ Alarm warnings in case of malfunction

Water Purification System characteristics for GMP environment

- Measurement and control sensors must be calibrated and the user must be able to prove it

  FDA GLP Maintenance and Calibration **(58.63 - a)**

  "Equipment shall be adequately inspected,cleaned and maintained. Equipment used for the generation, measurement or assessment of data shall be adequately tested, calibrated and/or standardised."

  ⇒ Calibration Certificates can be provided free of charge for all the measurement devices (conductivity, resistivity, temperature, TOC) if qualification package is bought.

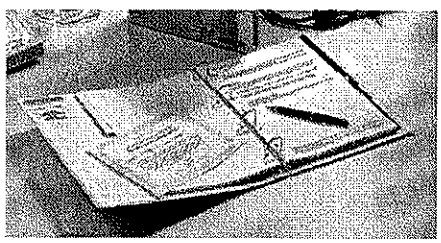
  ⇒ Consumable Quality Certificates can be provided on demand.

  ⇒ Certificate of Conformity is provided with each system.

Water Purification System characteristics for GMP environment

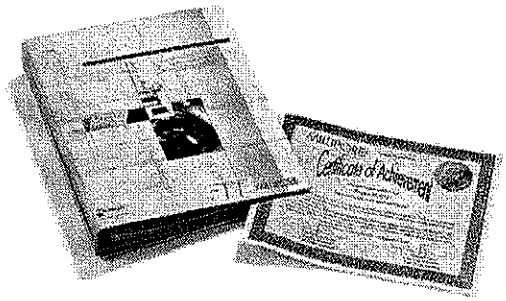
- Qualification protocol designed to answer to the GMP and Good Testing Practices requirements will be available.

  ⇒ Protocol designed to help users to completely and easily qualify their water system with 5 parts: Overview, IQ, OQ, MP, PQ



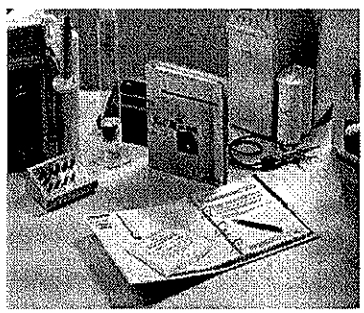
Water Purification System characteristics for GMP environment

- Customer Care Engineer trained to perform the Qualification (CFR 21 Parts 221.25 Personnel qualifications & 211.34 Consultants)



Water Purification System characteristics for GMP environment

- Calibrated test equipment available: calibrated Conductivity meter, calibrated Manometer, calibrated Measuring Cylinder, calibrated Stopwatch, Test box 3



Water Purification System characteristics for GMP environment

- Systems manufactured under quality management system (ISO, …) to permit traceability
  - All the Large Water Purification Systems are manufactured in our ISO 9001/ISO 14001 certified plant based in France



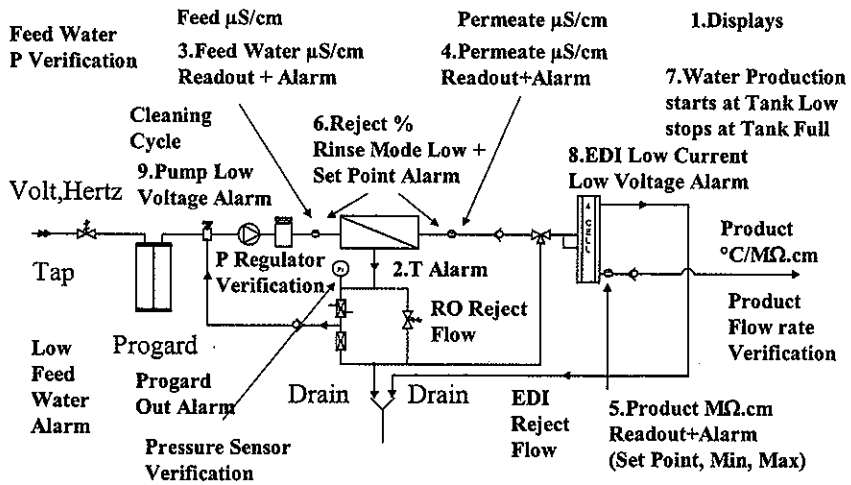
MILLIPORE
WATER PURIFICATION SYSTEMS
Certificate of Conformity

Catalogue N° Serial N°

This product has successfully passed all quality and performance criteria in accordance with applicable Millipore standard procedures and specifications.
This product was manufactured in Millipore S.A. 67120 Molsheim-France facility whose quality management system is approved by an accredited registering body to the ISO 9000 Quality Systems Standards : AFAQ Certificate N° 1991 / 240 b.

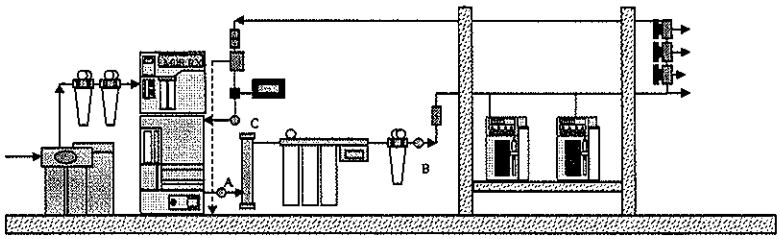
Brigitte Weber
Millipore S.A. Quality Assurance Manager

Elix Workbook



IQ - OQ Electronic - OQ Hydraulic - OQ Monitoring

System Workbook

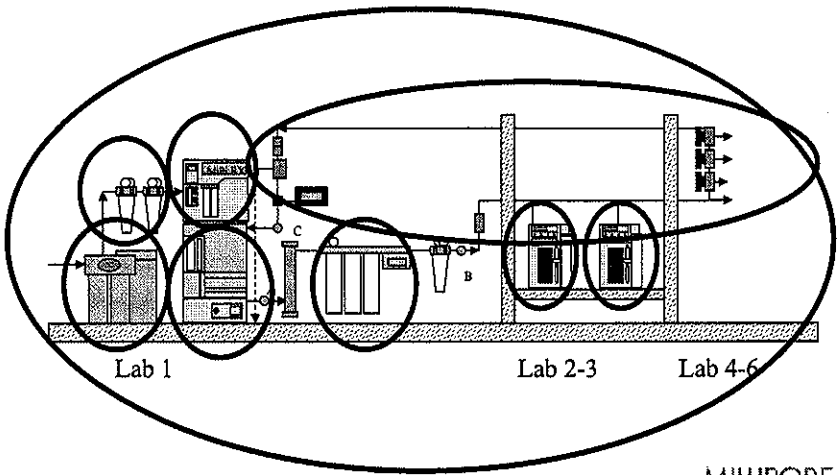


Lab 1 Lab 2-3 Lab 4-6

With passion comes dedication

MILLIPORE

System and Units Workbooks



Lab 1 Lab 2-3 Lab 4-6

With passion comes dedication

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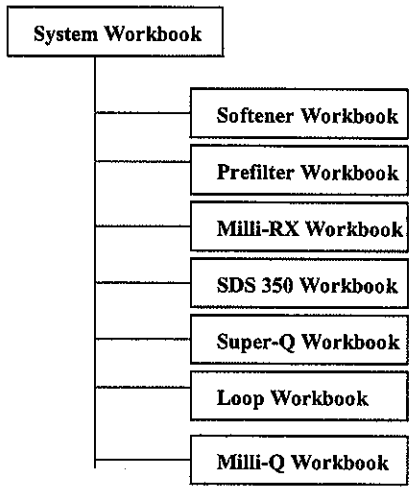
System Workbook



With passion comes dedication

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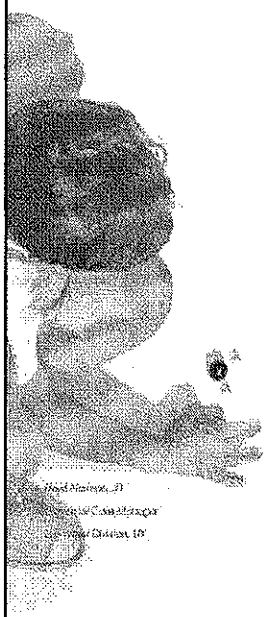


Conclusion

A turnkey Total Water Solution for the Laboratories

- Millipore's expertise, structure and offer gives the opportunity to the user to deal with only one company taking care of the project from the beginning to the end for guaranteed results and full peace of mind

MILLIPORE



With passion comes dedication

MILLIPORE

Case Studies and Applications

- Pharmaceutical Research Laboratory Building, Germany
- Pharmaceutical QC Laboratory Floor, Switzerland
- Pharmaceutical Production Area, Norway
- Sterilisation Department of a Hospital, France
- Biochemistry Laboratory of a hospital, United Kingdom
- Hospital Building, USA
- Micro-electronics Applications, Germany

MILLIPORE

- Pharmaceutical Research Laboratory Building, Germany
- Pharmaceutical QC Laboratory Floor, Switzerland
- Pharmaceutical Production Area, Norway
- Sterilisation Department of a Hospital, France
- Biochemistry Laboratory of a hospital, United Kingdom
- Hospital Building, USA
- Micro-electronics Applications, Germany

MILLIPORE

Pharmaceutical Research Laboratory building

- **Application**
  - Water for washing machine
  - Ultrapure water for HPLC and reagent preparation
- **Quality requirements**
  - Aqua purificata according to EP (European Pharmacopoeia
- **Amount of water needed**
  - 800 – 1000 L/day
- **Quality control**
  - It is essential for the customer to be sure of the water quality in the loop
    - Resistivity
    - TOC in the loop

Pharmaceutical Research Laboratory building

- Total solution concept
  - Elix 70
  - 1000 L reservoir
  - PP-loop for pure water distribution including
    - 0.22µm filter at loop departure
    - 0.22µm filter at the loop return
  - Milli-Q Gradient A10 for the Ultra-pure water needs

Pharmaceutical Research Laboratory building

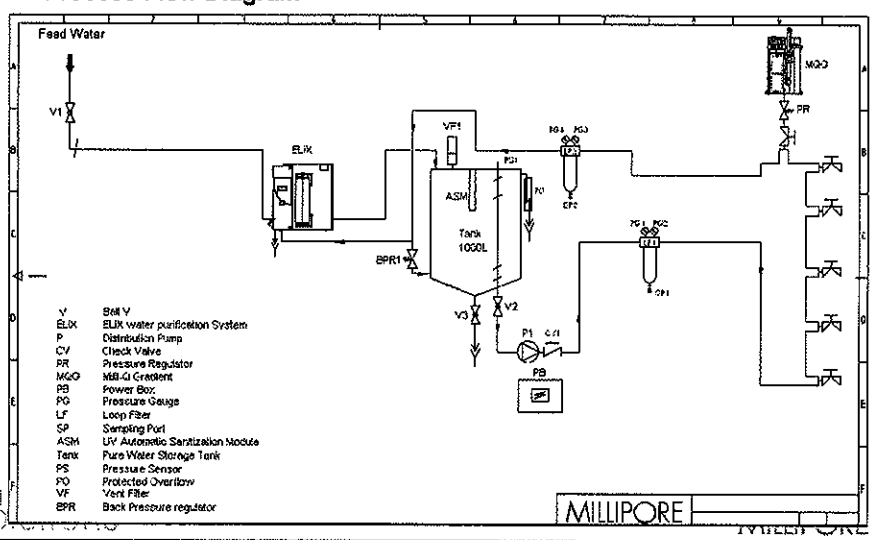
- Key Features
  - Pump CHI 2-60 with power-box (motor starter)
    - Pump is directly controlled by the Elix system
    - No need for a control box
  - Resistivity and TOC automatically monitored at the loop return by the Elix system
    - Loop return represents the worst case scenario
  - Automatic Sanitization Module
    - UV Sanitize the top of the tank 5 times per day
    - ASM is directly controlled by the Elix system

Total PureWater Solutions

MILLIPORE

Pharmaceutical Research Laboratory building

- **Process Flow Diagram**

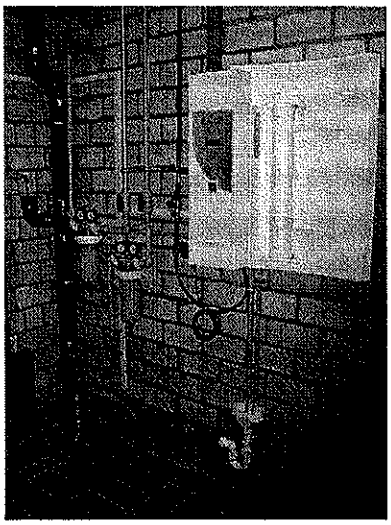


Total SOLUTIONS

MILLIPORE

Pharmaceutical Research Laboratory building

- Picture



Total PureWater Solutions

MILLIPORE

- Pharmaceutical Research Laboratory Building, Germany
- Pharmaceutical QC Laboratory Floor, Switzerland
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- Biochemistry Laboratory of a hospital, United Kingdom
- Hospital Building, USA
- Micro-electronics Applications, Germany

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Pharmaceutical QC Laboratory Floor

- **Application**
  - Water for 3 washing machines
  - Water for bacteriological culture media preparation
  - Ultrapure water for HPLC and reagent preparation
- **Quality requirements**
  - Aqua purificata according to EP (European Pharmacopoeia)
- **Amount of water needed**
  - 1500 L/day
  - Availability of the water is key as lots can be held if analyses can't be performed
- **Quality control**
  - It is essential for the customer to be sure of the water quality in the loop
  - Monitoring of the Resistivity and TOC at production + in the loop
  - Need to test the bacteriological water quality
  - Sanitary sampling valve

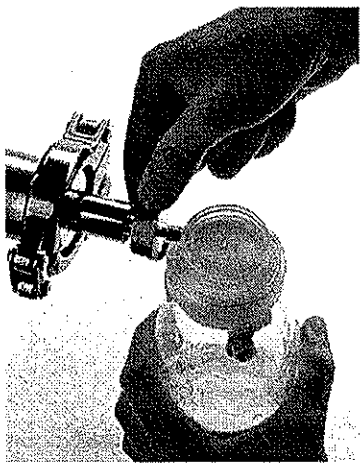
Pharmaceutical QC Laboratory Floor

- Total solution concept
  - 2 Elix 70 with 1000 l reservoir
  - Milli-Q Gradient A10 for the Ultra-pure water needs
  - 50m PPn-loop for pure water distribution including
    - 0.22µm filter at loop departure
    - 0.22µm filter at the loop return
  - ESP Sanitary Sampling valves
    - Combination with use of micropresure for complete solution
      - No risk of false positives

Pharmaceutical QC Laboratory Floor

- Key Features
  - Like for the Lab example
    - Pump is directly controlled by the Elix system
      - No need for a control box
    - Resistivity and TOC automatically monitored at the loop return by the Elix system
    - Automatic Sanitization Module
      - UV Sanitize the top of the tank 5 times per day
      - ASM is directly controlled by the Elix system
  - Duplex concept
    - One production module down for maintenance, the department still can work
  - No use of the duplex pump
    - Considered in the pharma world as potential source of bacteria contamination (second pump delivered as a spare)
  - Automatic dumping valve
    - Rejects water for fresh production if no water has been used in 24hours
  - Complete and reliable solution to monitor of the bacteria level

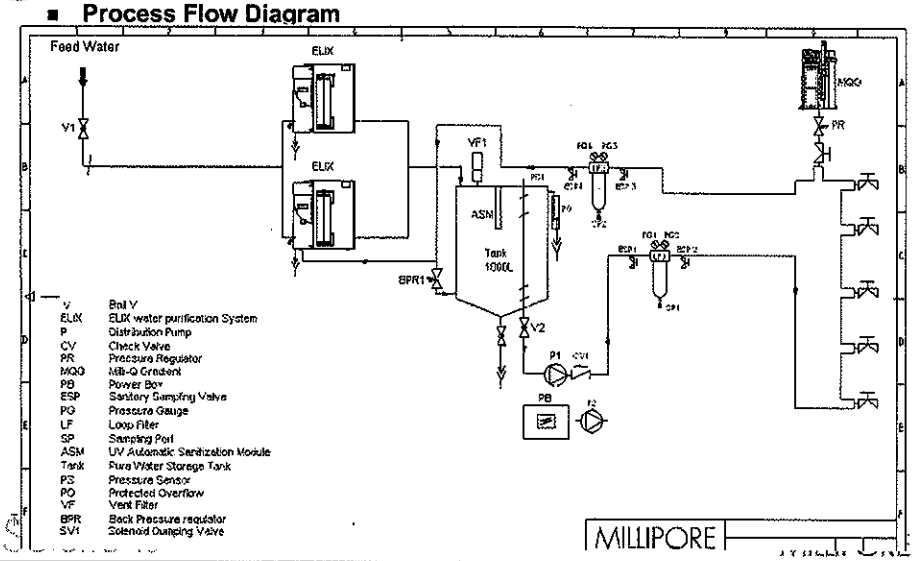
The Millipore Water Solution also includes MicropreSure for Bacteriological Analysis





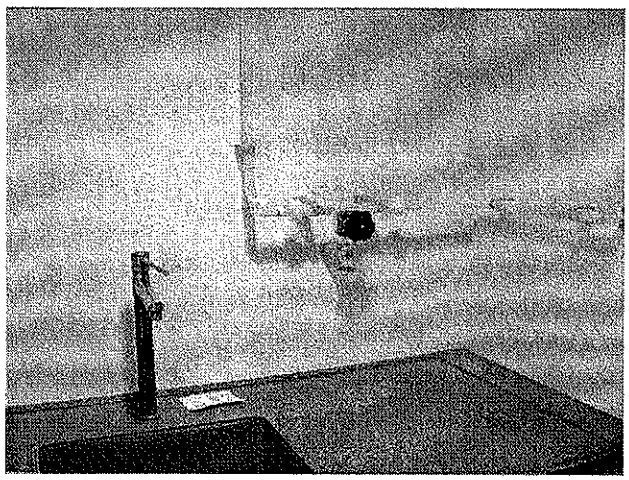
Pharmaceutical QC Laboratory Floor

- **Process Flow Diagram**



Pharmaceutical QC Laboratory Floor

- **Pictures**



Total PureWater Solutions

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- **Pharmaceutical Research Laboratory Building, Germany**
- **Pharmaceutical QC Laboratory Floor, Switzerland**
- **Pharmaceutical Production Area, Norway**
- **Sterilisation Department of a Hospital, France**
- **Biochemistry Laboratory of a hospital, United Kingdom**
- **Hospital Building, USA**
- **Micro-electronics Applications, Germany**

MILLIPORE

Pharmaceutical Production Area

- **Application**
  - A manufacturer of clinical diagnostic tests on membrane strips for qualitative or semi-quantitative measure of important human biological parameters such as albumin in urine or glycosilated hemoglobin in blood need UP for their production
- **Amount of water needed**
  - 2000 L/day
  - Availability of the water is key as production depends on water
- **Quality control**
  - It is essential for the customer to be sure of the water quality in the loop
  - Monitoring of the Resistivity and TOC at production + in the loop
  - Need to test the bacteriological water quality

Total PureWater Solutions

MILLIPORE

Pharmaceutical Production Area

- **Quality requirements**

Loop

Parameter	Unit	Alert level	Action Level
Conductivity (loop)	µS/cm	> 1.3	> 3
TOC (loop)	ppb	> 50	> 500
Bacteria (loop)	cfu / 100 ml	> 10	> 50

Milli-Q

Parameter	Unit	Alert level	Action level
Resistivity	MΩ.cm à 25°C		< 18.2
Bacteria	Cfu / 100 ml	> 10	> 20

- The endotoxin level must also be under control

Total PureWater Solutions

MILLIPORE

Pharmaceutical Production Area

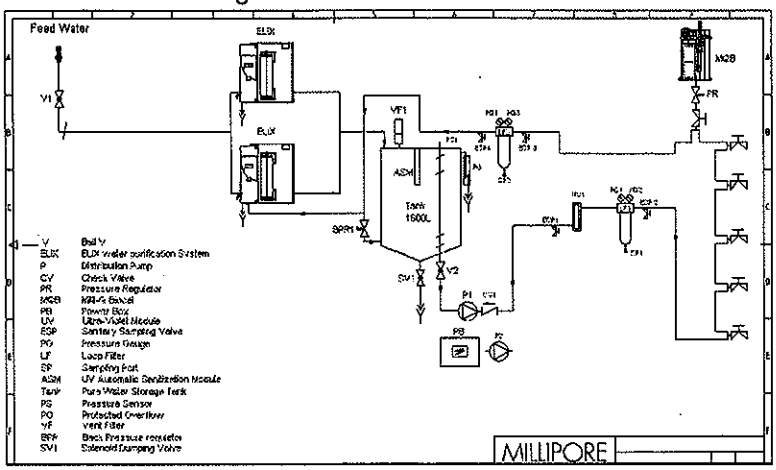
- Total solution concept
  - 2 Elix 70 Duplex for insurance of water being available
  - 1600 L reservoir
  - 150m PPn-loop for pure water distribution including
    - Charged 0.22µm filter at loop departure
    - Charged 0.22µm filter at the loop return
  - ESP Sanitary Sampling valves
  - Milli-Q Gradient A10 for the Ultra-pure water needs

Total PureWater Solutions

MILLIPORE

Pharmaceutical Production Area

- Process Flow Diagram



Total PureWater Solutions

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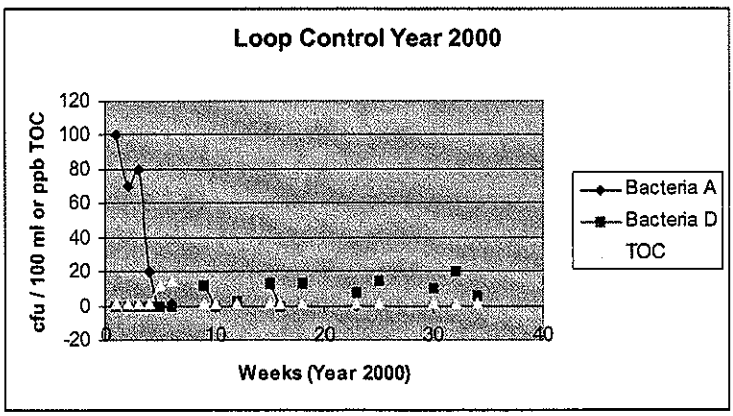
Long Term Control

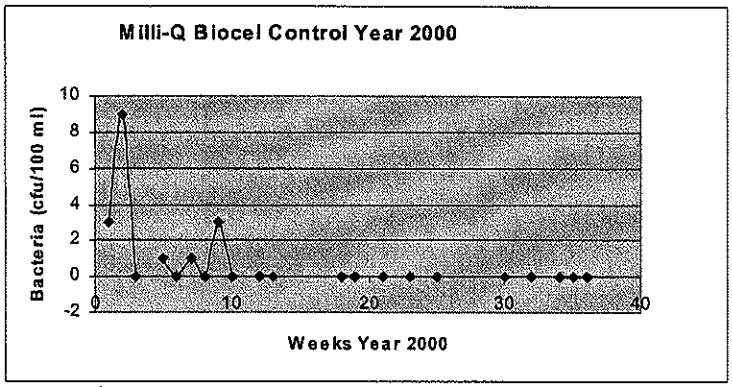


Loop Conductivity was always below 1.3 µS/cm

Total PureWater Solutions

MILLIPORE

Milli-Q Biocel Bacteriology Control (PQ)



Pharmaceutical Production Area

- Key Features
  - Like for the other examples
    - Pump is directly controlled by the Elix system
      - No need for a control box
    - Resistivity and TOC automatically monitored at the loop return by the Elix system
    - Automatic Sanitization Module
      - UV Sanitize the top of the tank 5 times per day
      - ASM is directly controlled by the Elix system
    - Duplex concept
      - One production module down for maintenance, the department still can work
    - Automatic dumping valve
    - Complete and reliable solution to monitor of the bacteria level
  - Charged Durapore in the distribution loop to lower the level of bacteria
  - Full Qualification performed by Millipore trained service force

- **Pharmaceutical Research Laboratory Building, Germany**
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- **Hospital Building, USA**
- **Micro-electronics Applications, Germany**

MILLIPORE

Sterilization Department of a Hospital

- **Application**
  - Sterilization Department of the biggest Children Hospital in Paris, France needed to their 4 feed autoclaves daily.
    Water is critical as no water means no sterilization of the tools needed for surgery
- **Amount & quality of the water needed**
  - 3000 L/day of RO water (type III)
  - Regulation to follow : EN 285 (15 µS/cm max.)
    - Too good of a water could "eat up" the heating element of the autoclave
- **Quality control**
  - Conductivity of the water produced
  - Have access to the operating parameters of the water purification system

Total PureWater Solutions

MILLIPORE

Sterilization Department of a Hospital

- Total solution concept
  - 2 Rios 100 Duplex for insurance of water being available
  - 1000 L reservoir
  - 50m PP-loop for pure water distribution including
    - 0.22µm filter at loop departure
  - Duplex distribution pumps

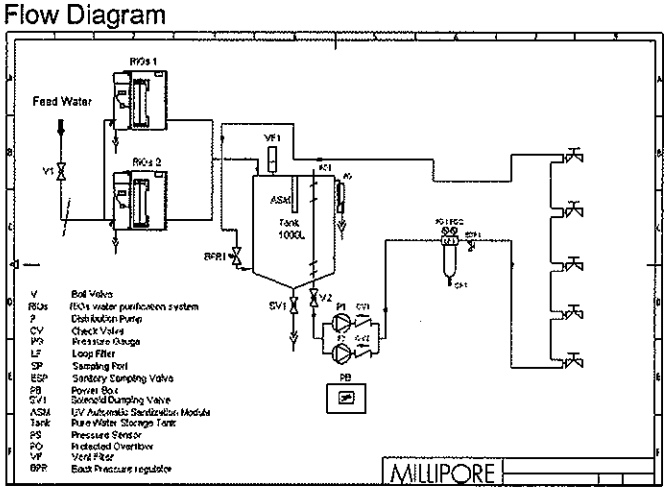
- Key Features
  - Adapted water quality to the specific applications
  - Duplex production modules and duplex distribution pumps to be sure of water availability at all times
  - Possibility to recover once a month all the parameters of the system and store them in a file

Total PureWater Solutions

MILLIPORE

Pharmaceutical Production Area

- Process Flow Diagram



Total PureWater Solutions

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- **Hospital Building, USA**
- **Micro-electronics Applications, Germany**

MILLIPORE

Biochemistry Lab of a Hospital

- **Application**
  - Feed several 4 clinical analyzers that routinely perform analyses on a 8 hour shift
  - Occasionally for the need of the lab other applications (buffer preparation, reagent preparation) some additional liters are needed
- **Amount & quality of the water needed**
  - 2500 L/day of type II analytical grade water
  - Regulation to follow : NCCLS type II water
- **Quality control**
  - Resistivity of the water produced

Total PureWater Solutions

MILLIPORE

Biochemistry Lab of a Hospital

- Total solution concept
  - 2 Elix 100 Duplex for insurance of water being available
  - 1000 L reservoir
  - 20m ABS-loop for pure water distribution including
    - ABS is very much used in the UK (PP is usually considered as a better choice as no glue is involved)
  - Duplex distribution pumps

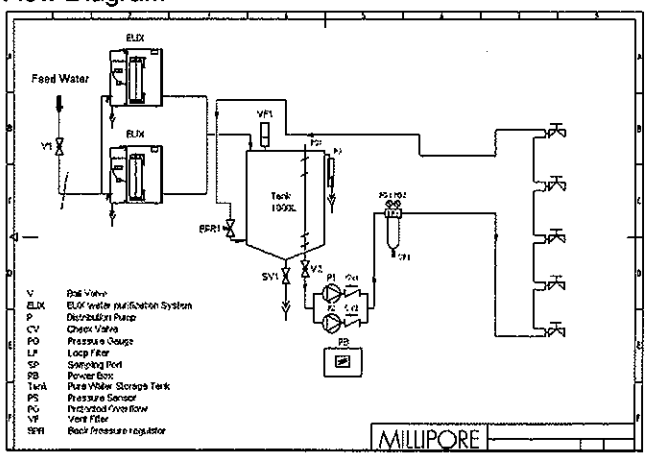
- Key Features
  - Adapted water quality to the Analyzer Specifications
  - Duplex production modules and duplex distribution pumps to be sure of water availability at all times
  - Reasonable running cost compared to other envisioned solutions

Total PureWater Solutions

MILLIPORE

Biochemistry Lab of a Hospital

- Process Flow Diagram



Total PureWater Solutions

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- **Hospital Building, USA**
- **Micro-electronics Applications, Germany**

MILLIPORE

Hospital Building Solution

- **Application**
  - Feed a 8 Lab floor Building with appropriate water quality
- **Amount & quality of the water needed**
  - Determined with each lab manager in partnership with the A&E company
  - As an average 1000 L of type II water per floor
  - Needs for Ultra Pure water at specific points of use
- **Quality control**
  - Resistivity of the water produced

Total PureWater Solutions

MILLIPORE

Hospital Building Solution

- Total solution concept
  - Floor by floor approach (each install takes care of 2 floors)
    - 2 Elix 70, Duplex for insurance of water being available
    - 1000 L reservoir
    - 200m PP-loop for pure water distribution
- Key Features
  - Concept answered all the customer's requests/concerns

Total PureWater Solutions

MILLIPORE

Total Water Purification System
Approach 2; By Floor or by Department



Total PureWater Solutions

MILLIPORE

Key Points for the customer

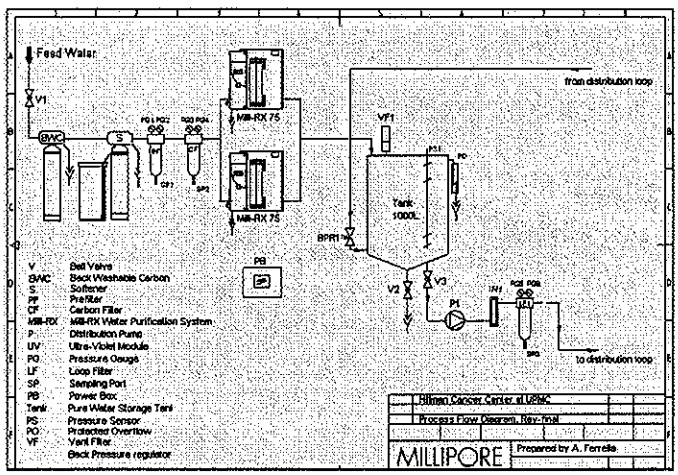
- Insurance that they won't lack water
- Easier maintenance
- Easier to sanitise
- Less bacteriological analysis
  - process once a day but depending of the lab: test once a week or even less
- Better quality/price ratio

Total PureWater Solutions

MILLIPORE

Hospital Building Solution

- Process Flow Diagram



Total PureWater Solutions

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- **Hospital Building, USA**
- **Micro-electronics Applications, Germany**

MILLIPORE

Technical University of Berlin
Institute of Physics - Centre of Nanophotonics

- **Application**
  - Wafer rinsing
  - Final rinse for a washing machine
- **Requirements**
  - Pure water for feeding a washing machine and an ultrapure water system
  - Ultrapure water for feeding a wet-bench a washing machine and 2 other rinsing equipments
  - Rinsing water from the wet-bench depending of the quality must not be dumped Quality-control by the wet-bench

Total PureWater Solutions

MILLIPORE

Technical University of Berlin
Institute of Physics - Centre of Nanophotonics

- **Quality requirements**
  - Pure water: no special requirements just as good as possible for the ultrapure water system
  - Prevent of bacteria growth
  - Ultrapure water:
    - 18.2 MOhm.cm
    - TOC < 50 ppb
    - Flowrate: 20 l/min with 4-5 bar
- **Amount of water needed**
  - 1200 l/d
- **Quality control**
  - Resistivity and TOC in the loop

Total PureWater Solutions MILLIPORE

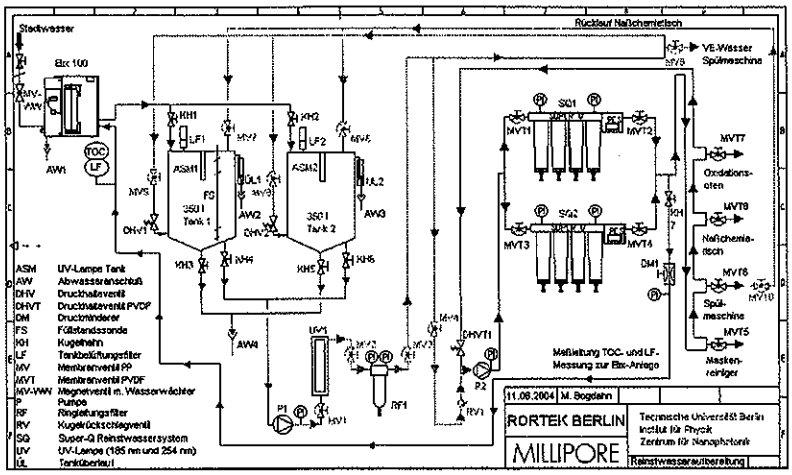
Technical University of Berlin
Institute of Physics - Centre of Nanophotonics

- **Total solution concept**
  - Elix 100 with 2 SDS 350 in parallel
  - ASM
  - 1 PP-loop for pure water distribution including a UV-Lamp (185 and 254 mn) and a 0,22 µm filter
  - 1 PVDF loop for ultra-pure water with second distribution pump
    - 2 Super-Q systems in parallel
  - TOC- and Resistivity-measurement in the ultra-pure water loop after the Super-Qs directly by the Elix-system
  - 2 CHI 2-60 pumps, (one for each loop)
  - Pumps and UV-Lamp are controlled and powered by the Elix-control board
  - Resistivity- and TOC-Kit for Elix-system

Total PureWater Solutions MILLIPORE

Technical University of Berlin
Institute of Physics - Centre of Nanophotonics

- **Process Flow Diagram**



Total PureWater Solutions

MILLIPORE

Technical University of Berlin
Institute of Physics - Centre of Nanophotonics

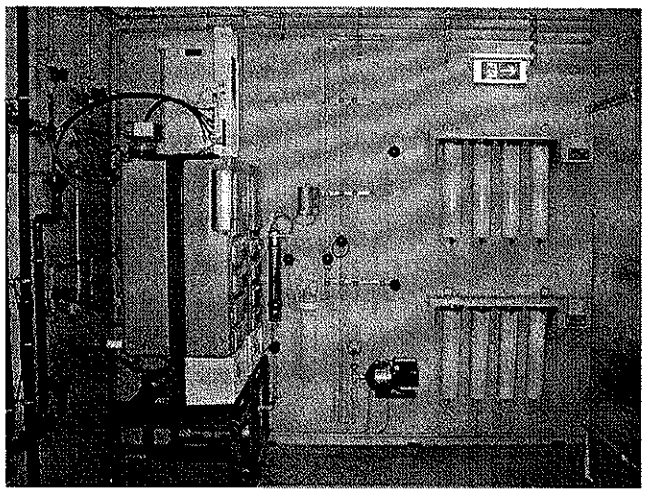
- **Key Features**
  - Resistivity and TOC in the loop
  - Two water Qualities available
  - High flow polishers in the second loop to meet ultra-pure water requirements
    - Selection of PP for type II water and PVDF for Ultrapure water
  - UV Lamp in the loop to lower the TOC and bacteria removal

Total PureWater Solutions

MILLIPORE

Technical University of Berlin
Institute of Physics - Centre of Nanophotonics

- **Pictures**



Total PureWater Solutions

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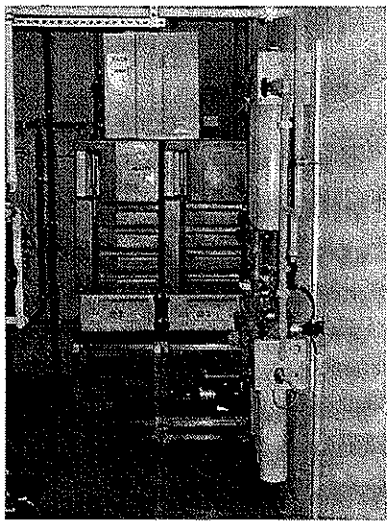

Total PureWater Solutions

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