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PHARMACEUTICAL GRADE WATER

制药用水

TRAINING SESSION

Drinking water is the starting material to produce the “Waters” for Pharmaceutical Industry.
饮用水是生产制药用水的源水。

The performances of the equipment to generate the waters are subjected to drinking water quality, and its fluctuations must be considered individually.
制水设备的性能与饮用水的水质相关，所以水质的波动必须单独考虑。

regional variations in quality
水质的地域差异

- daily / yearly water quality variations
  每天/每年的水质变化
- temperature fluctuations
- 水温的波动
- recontamination through the pipe network
- 通过管网的再污染

Water Specification水的标准

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	PW (Ph. Eur.) 纯化水	**PW** (USP) 纯化水	**HPW / WFI *** 高纯水/注射用水
pH 酸碱度	5 – 7	5 – 7	5 – 7
NITRATE 硝酸盐	< 0,2 ppm	-	< 0,2 ppm
Heavy Metals 重金属	< 0,1 ppm	-	< 0,1 ppm
TOC 总有机碳	⩽ 500 ppb	⩽ 500 ppb	⩽ 500 ppb
Conductivity 电导率	⩽ 4,3 µ S/cm (20 ° C)	⩽ 1,3 µ S/cm (25 ° C)	1,1 µ S/cm (20 ° C)
Plate count 微生物限度	< 100 cfu/ml (R2A)	< 100 cfu/ml (PC)	< 10 cfu/100 ml (R2A)
Endotoxine 内毒素	-	-	< 0,25 EU/ml

Purified Water 纯水Highly Purified Water 高纯水Water for injections 注射用水

* WFI (Ph. Eur.) Only by distillation!! 欧洲药典只允许蒸馏法制取

Water Specification水的标准

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Examples of use 使用举例	**PW** (Ph.Eur.)	**PW** (USP)	**HPW**	**WFI** *
Cleaning and rinsing of Production facilities 生产设备清洁和冲洗	X	X		
Manufacturing and sterile生产和灭菌 non-sterile products 非无菌产品 external use 外部使用	X	X	X	
Manufacture of sterile products (Parenteral) 无菌产品的生产（非肠胃的）				X
Final Rinse 最后冲洗	X	X	X	

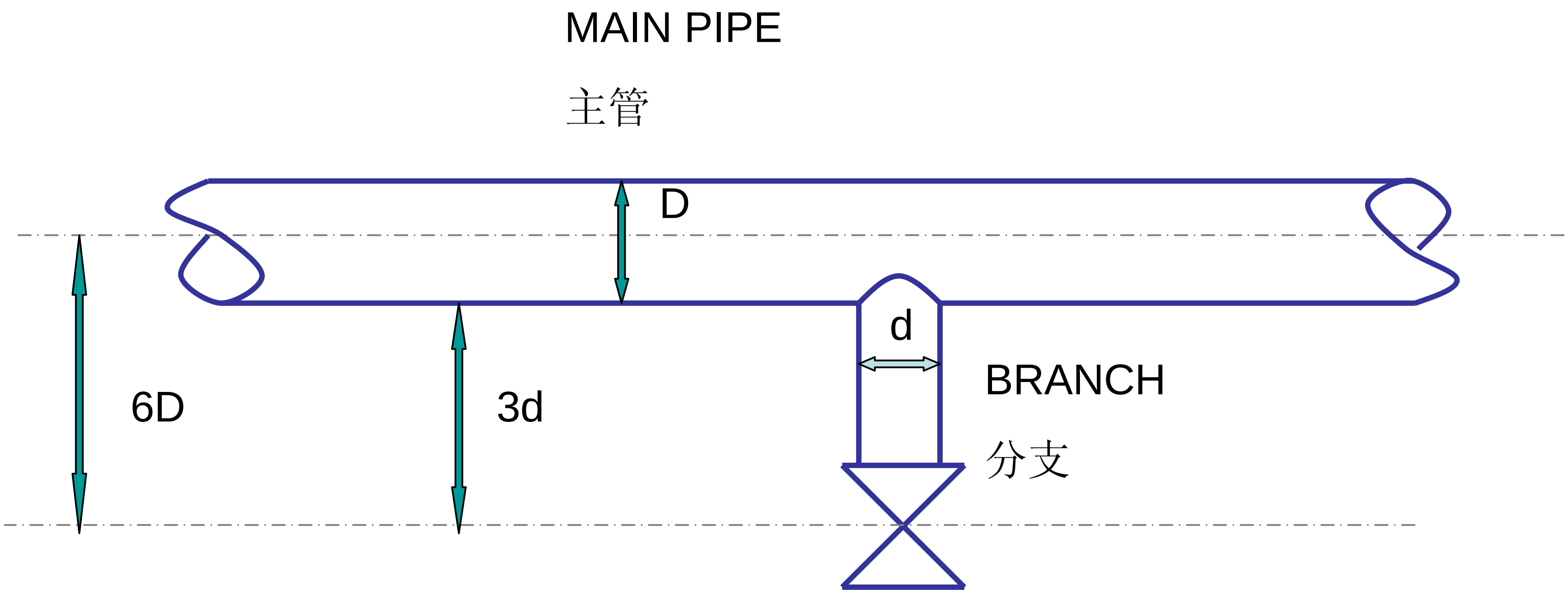
General Principles for Design (PW SIDE)
设计的基本原则（纯化水）

General Principles to Design (PW SIDE)
设计的基本原则

- Dead space free design (6D)
- 无死区设计
- Pipeline connections
- 管线连接
- Smooth surface, Ra <0.8 micron (PW side)
- 光滑的表面，表面光洁度<0.8 微米（纯化水）
- Application of appropriate welding process (e.g. orbital for stainless steel)
- 应用合适的焊接工艺（如不锈钢的轨道焊接）
- Valves, gauges and pumps in hygienic design
- 阀，仪表和泵的卫生设计
- Removal of residual = drainability (slope> 1%)
- 残留物的去除＝排水能力（坡度>1%)
- Use of appropriate materials (SFDA compliant)
- 合适材料的使用（符合SFDA)
- Continuous flow (circuit)
- 连续流动（回路）
- No sharp curves
- 无急弯
- Turbulent flow (Reynolds number Re> 2,400, practice> 0.5 m / s)
- 湍流（雷诺数>2,400, 惯例 > 0.5 m/s）
- Cold storage <20 ° C, heat soak 70 ° C
- 冷藏 <20 ° C，热储 70 ° C

RULE OF 6D (3d)

6D（3D)原则



WATER PRODUCTION

水的制备

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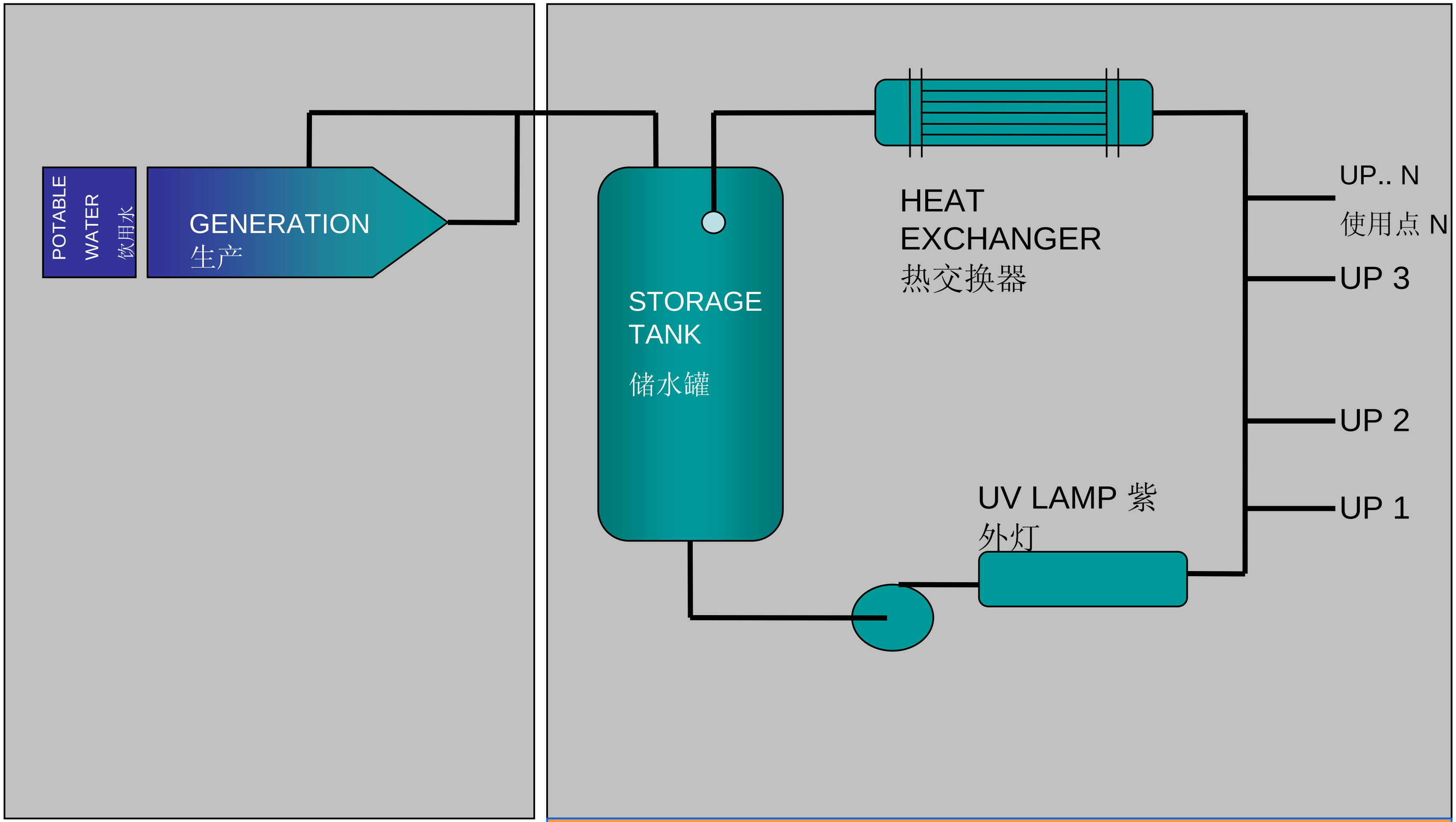
	PW纯化水	HPW高纯水	WFI注射用水
DISTILLATION 蒸馏	X	X	X
DEIONIZATION 去离子	X	-	
DOUBLE PASS R.O. 二级反渗透	X	X	X*
R.O. + CEDI 反渗透＋电渗析	X	-	-
R.O. + CEDI + UF 反渗透＋电渗析＋超滤		X	X*

Selection Criteria选用标准

	Advantage优点	Disadvantage缺点
Distillation 蒸馏法	Germ and pyrogen free无细菌和热原	High investment and operating costs 投入和运行成本高 carryover of volatile organics会夹带挥发性有机物
Ion exchange 离子交换法	low operating cost 费用低廉 Flexible range 耗能范围灵活 high salt retention 置换大量离子	chemical regeneration 化学再生 neutralization of sewage 排放需中和 microbiological load 微生物负载大 Discontinuous process 间断性生产
2 Pass RO 二级反渗透	Inexpensive 价格适中 Retention of bacteria and pyrogens 截留细菌和热原	Ion slip有离子透过 Possible additional pretreatment 可能需要预处理 high volumes of effluent 废水量大
RO CEDI 反渗透＋电渗析	high purity高纯度 low energy低能耗	Possible additional pre-treatment可能需要预处理 (CO_2-Entrapment)吸收二氧化碳
RO CEDI UF 反渗透＋电渗析＋超滤	highest retention of Bacteria and pyrogens除菌和除热原能力最强 low operating costs 低运行成本	Possible additional pre-treatment可能需要预处理 (CO_2-Entrapment) 吸收二氧化碳

Sanitization消毒



Chemical化学品 (H_2O_2)

Thermal热力 (Hot Water热水 80C)

Chemical化学品 (H_2O_2)

Thermal热力 (hot Water热水 80C, Steam蒸气)

Ozone臭氧

Sanitary Valve

卫生阀

No recesses – no hidden volume

无凹点－无死体积

Completely drainable

完全可排空

Resistant to heat (for sanitization)

耐热（消毒）

Sanitary Pumps

卫生泵

No recesses – no hidden volume

无凹点－无死体积

Completely drainable

完全可排空

Resistant to heat (for sanitization)

耐热（消毒）

Double mechanical seal fed with the same PW

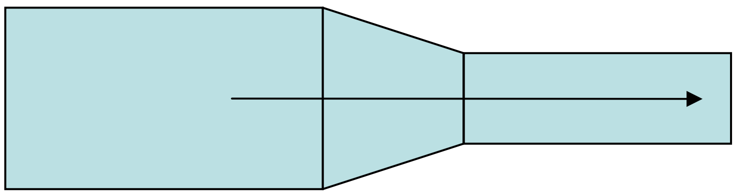
同一的纯水供给的双面机械密封

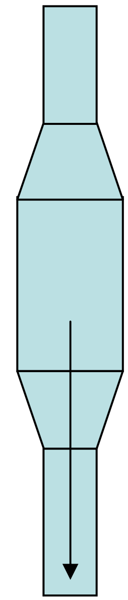
Size reduction – enlargement

尺寸减少一扩大

Concentric reduction 同轴缩小

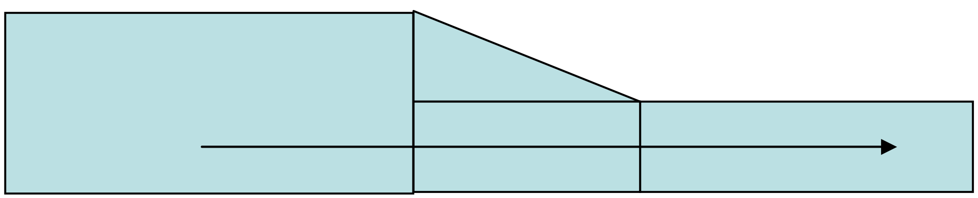
Drainable only in vertical 仅垂直下排空





Eccentric reduction 非同轴缩小

Drainable 可排空



BEFORE TREATING THE WATER IN A R.O. UNIT OR DESTILLATION COLUMN A PRE-TREATMENT IS SOMETIMES NECESSARY, DEPENDING ON THE FEED WATER CONDITIONS

根据进水情况，在水进入反渗透单元或蒸馏塔之前进行预处理有时是必要的。

MULTY LAYER FILTER 多层过滤器	Remove Suspended Solids除去悬浮物	General cleaning 简单清洁
CARBON FILTER 活性炭过滤	Remove Free Chlorine去除游氯	To preserve RO lifespan 保护反渗透膜寿命
SOFTENING 软化器	Ion substitution – antiscaling离子交换－防止结垢	To better operate with RO 更好地运行反渗透装置
ION EXCHANGE (CATIONIC / ANIONIC / MIXED BED) 离子交换（阳离子、阴离子、混床）	Deionization去离子	To better preserve the RO unit lifespan 更好地保护反渗透膜寿命

PRE TREATMENT前处理

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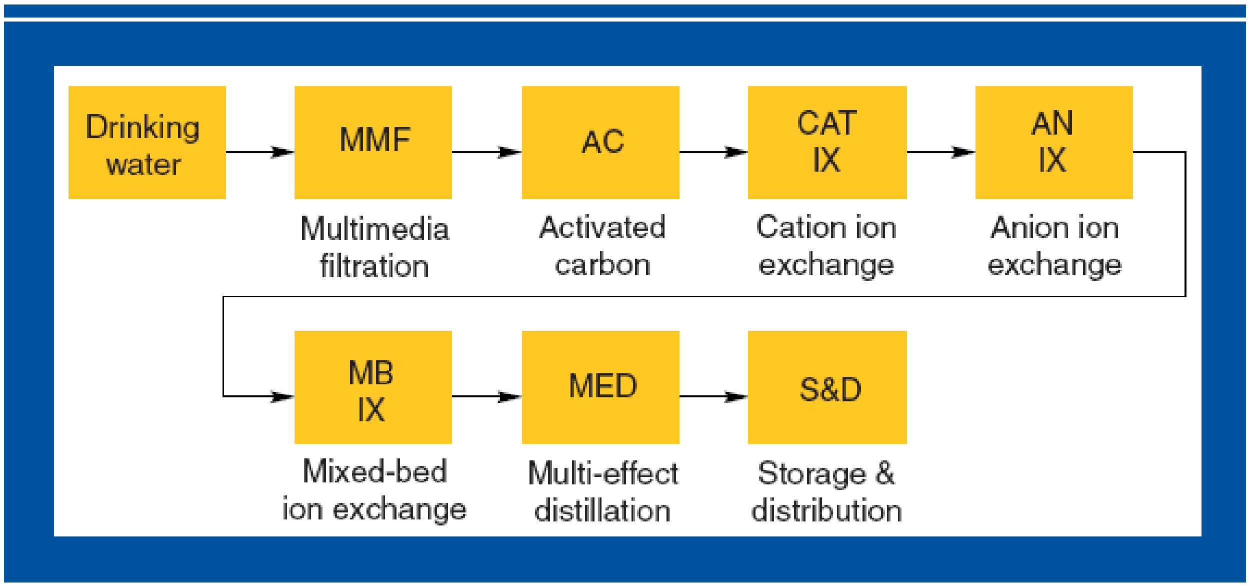

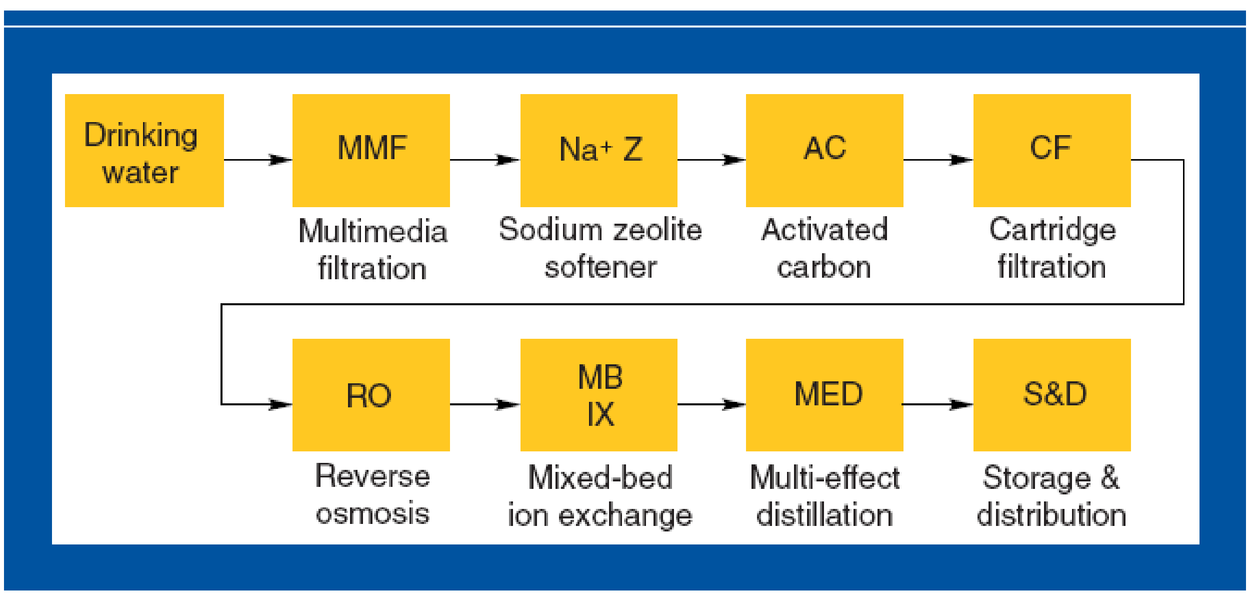

PRE TREATMENT前处理

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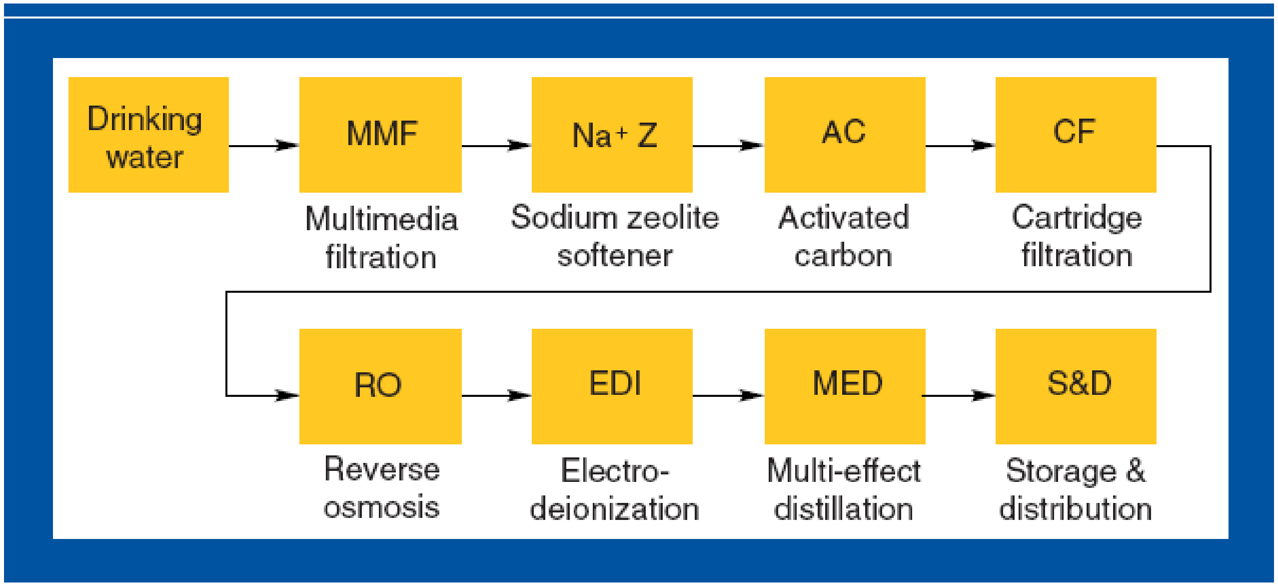

REVERSE OSMOSIS反渗透

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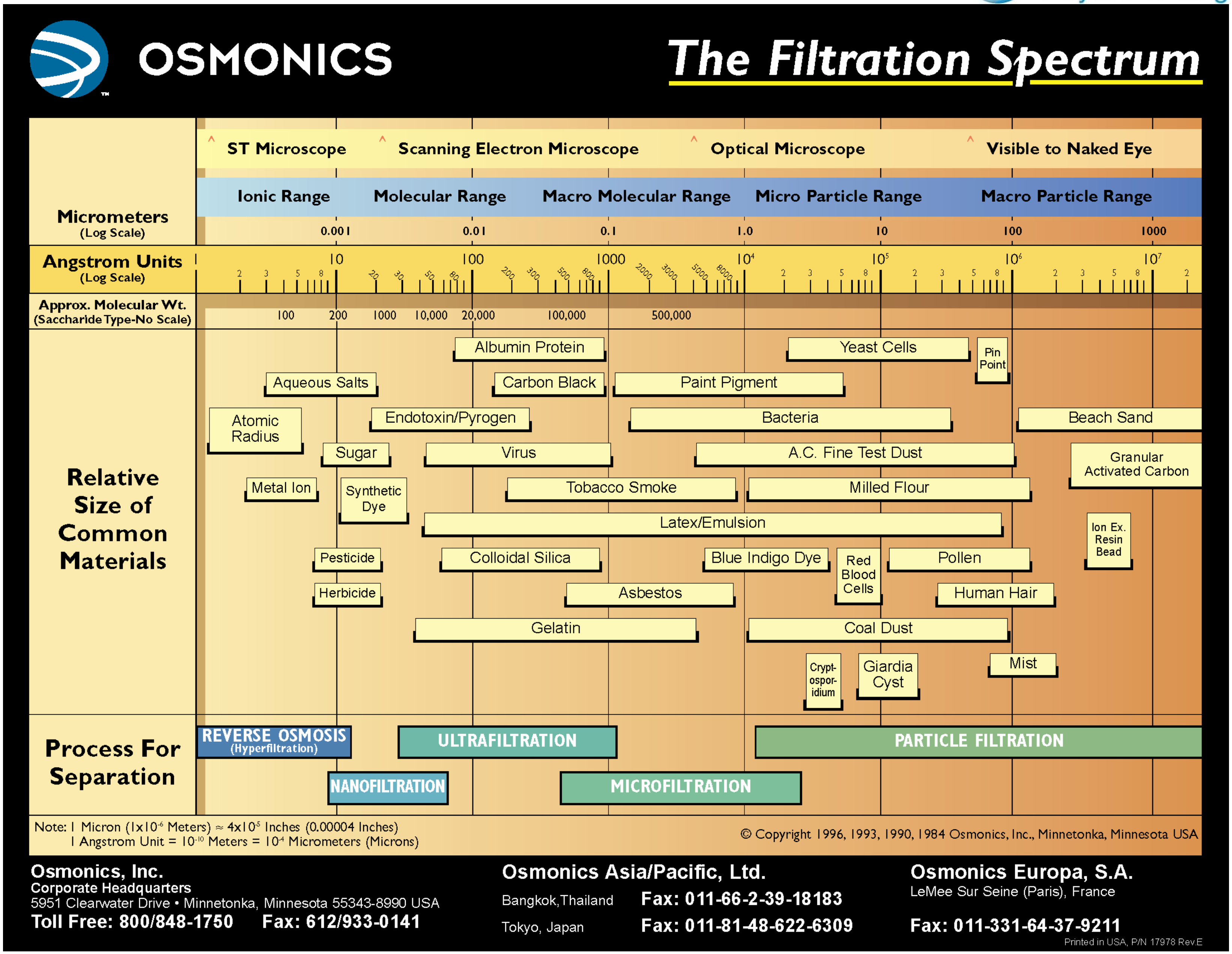

REVERSE OSMOSIS 反渗透

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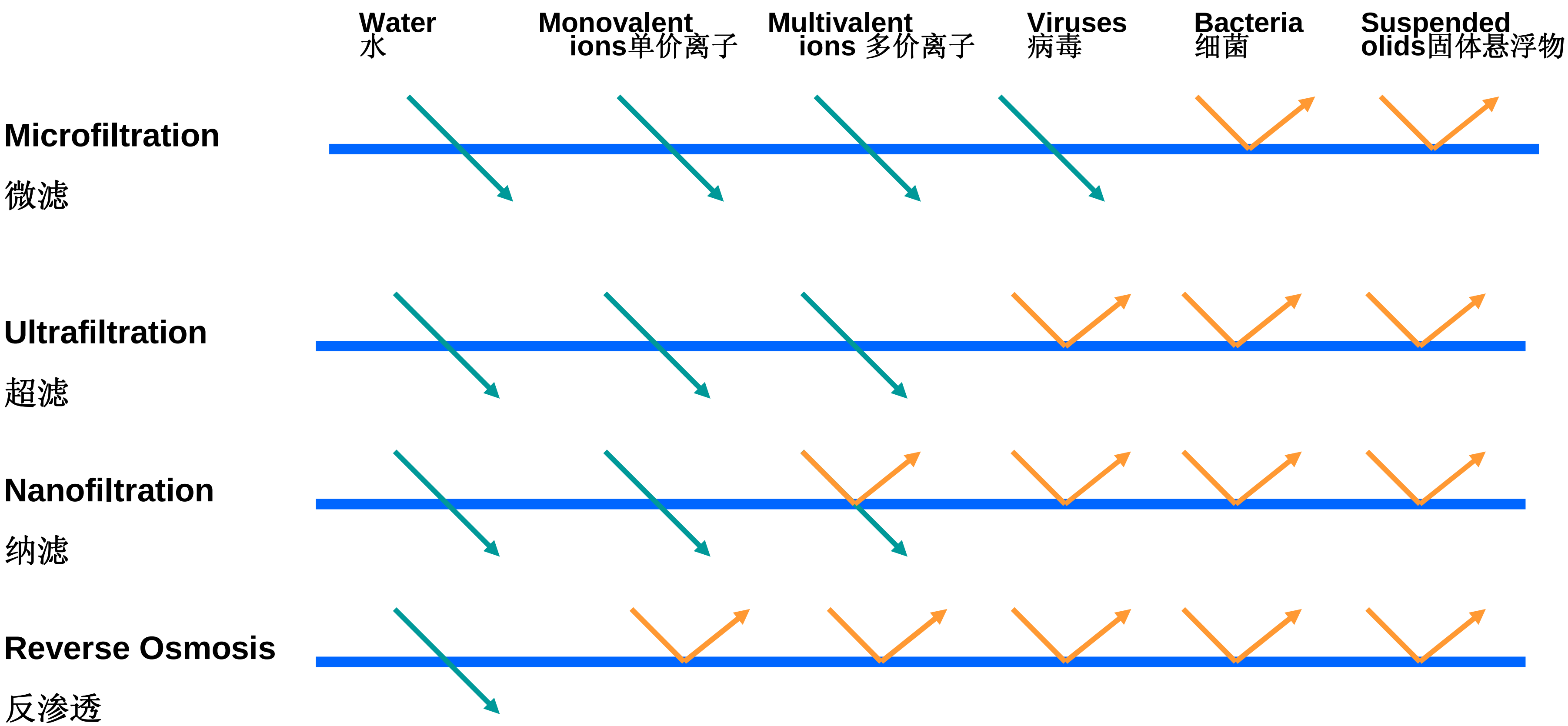

HOW REVERSE OSMOSIS WORKS反渗透如何工作

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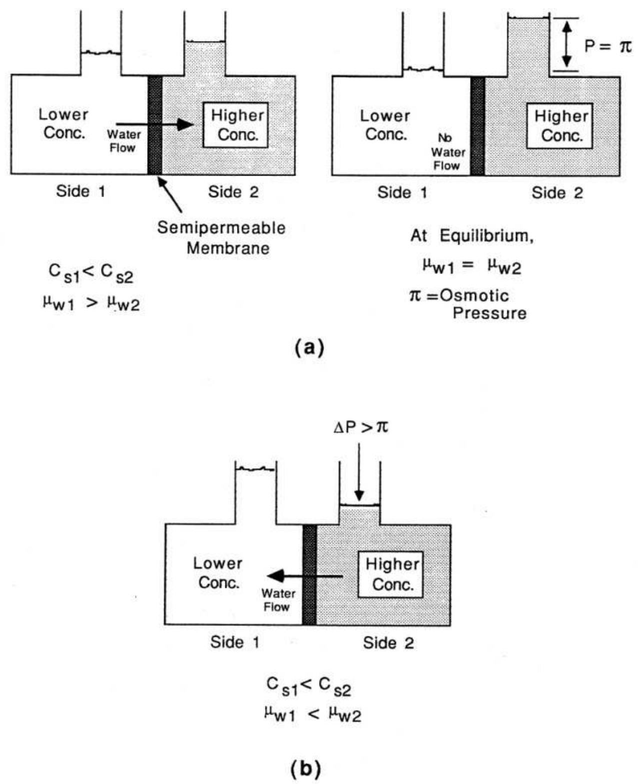


Figure 1. Schematic of Osmosis and Reverse Osmosis Phenomena.

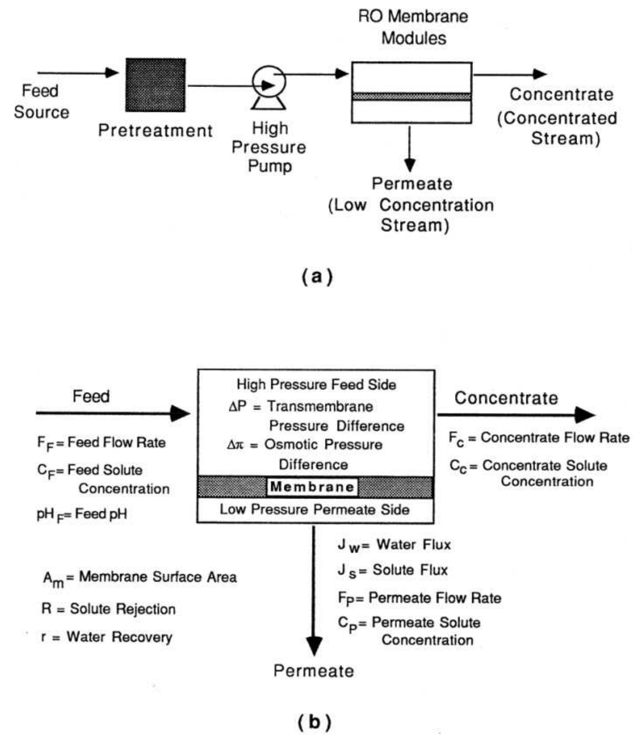
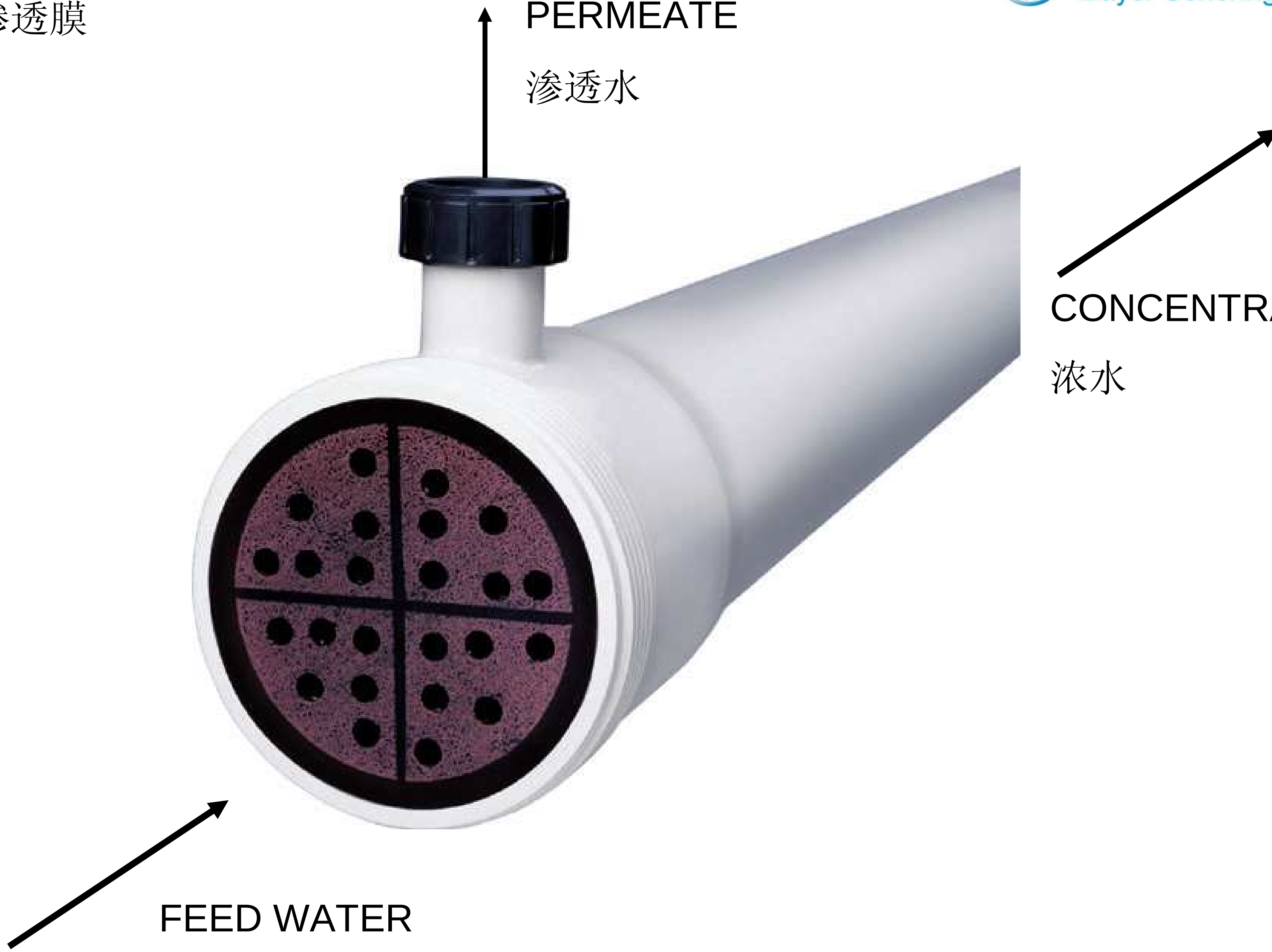


Figure 2. Schematic of (a) RO Membrane Process and (b) RO Process Streams.

R.O. Membranes

反渗透膜



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Common membrane materials include
通常膜的材料包括

polyamide thin film composites (TFC),
cellulose acetate (CA) and
cellulose triacetate (CTA)
聚酰胺复合膜，醋酸纤维素膜和三乙酸纤维素膜

with the membrane material being spiral wound around a tube, or hollow fibres bundled together.
膜材料螺旋盘绕在管子上，或与中空纤维捆在一起。

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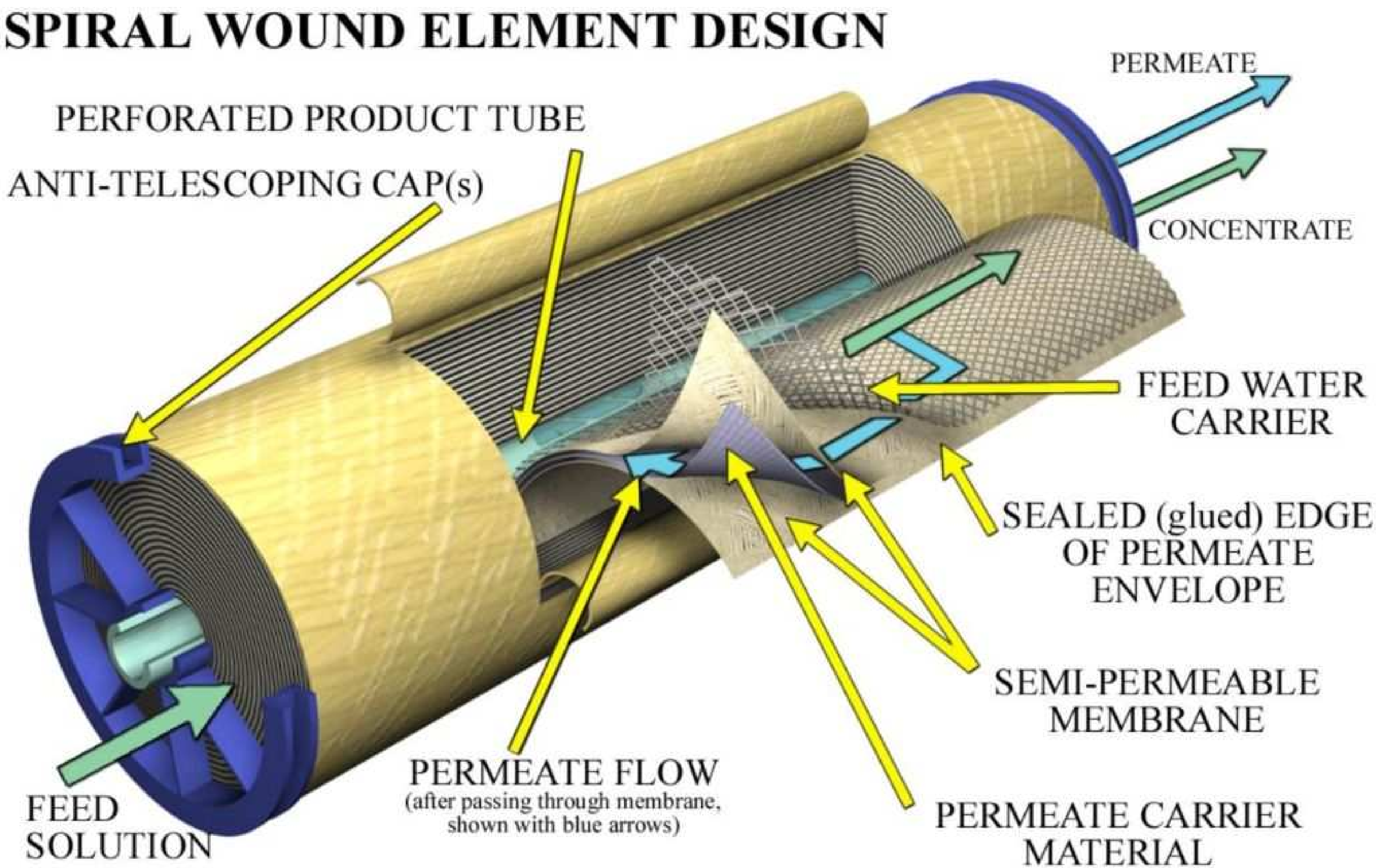
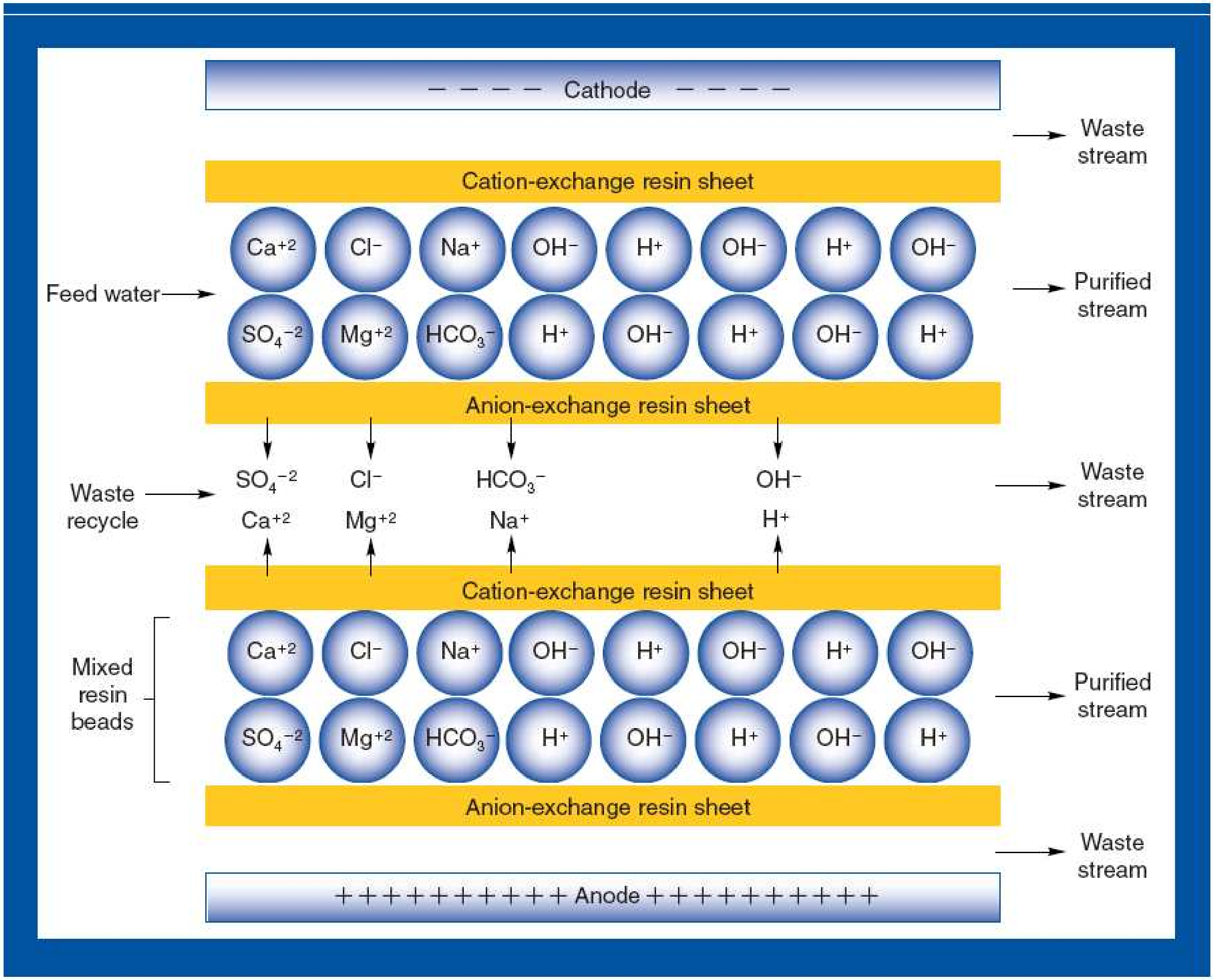


EDI 电渗析



– – – – Cathode – – – –
Waste stream
Cation-exchange resin sheet
Ca+2
Cl–
Na+
OH–
H+
OH–
H+
OH–
Feed water
Purified stream
SO4–2
Mg+2
HCO3–
H+
OH–
H+
OH–
H+
Anion-exchange resin sheet
Waste recycle
SO4–2
Cl–
HCO3–
OH–
Ca+2
Mg+2
Na+
H+
Waste stream
Cation-exchange resin sheet
Mixed resin beads
Ca+2
Cl–
Na+
OH–
H+
OH–
H+
OH–
Purified stream
SO4–2
Mg+2
HCO3–
H+
OH–
H+
OH–
H+
Anion-exchange resin sheet
Waste stream
+ + + + + + + + + + Anode + + + + + + + + + +

WFI – MULTIPLE EFFECT DISTILLATION

注射用水－多效蒸馏

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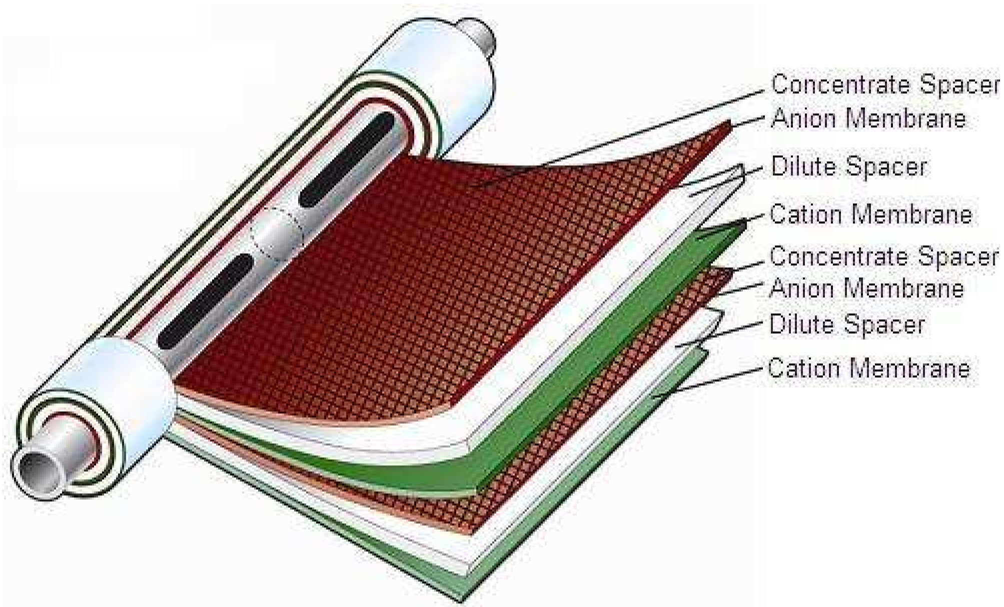
In a Multiple Effect Distillation the water is distilled only once.

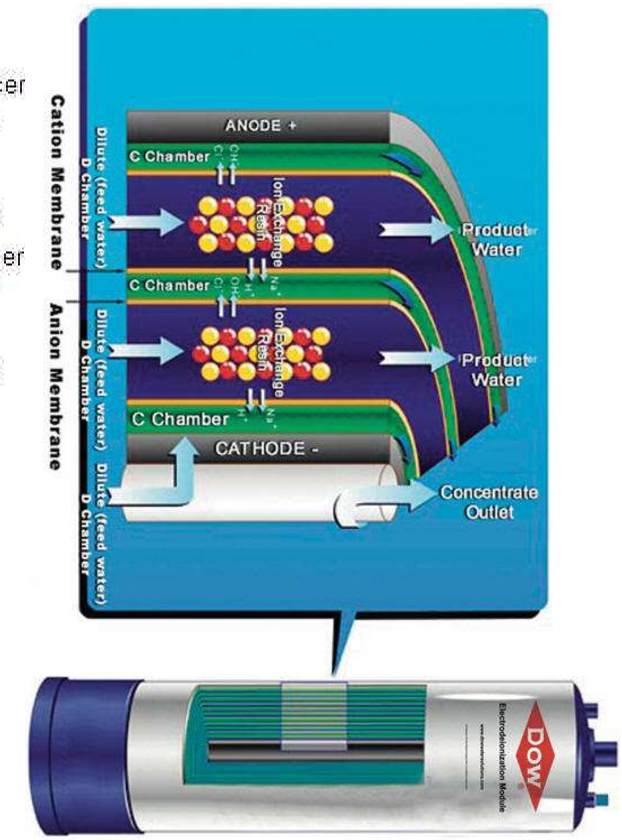
水在多效蒸馏中只蒸馏一次。

Multiple effect refers to the clean steam used in multiple stages to evaporate the water. It is determined by economical reasons.

多效是指用洁净的蒸汽在多个阶段使水蒸发。它是由经济原因决定的。

EDI 电渗析


Concentrate Spacer
Anion Membrane
Dilute Spacer
Cation Membrane
Concentrate Spacer
Anion Membrane
Dilute Spacer
Cation Membrane


ANODE +
C Chamber
Ion Exchange Resin
Product Water
C Chamber
Ion Exchange Resin
Product Water
C Chamber
CATHODE -
Concentrate Outlet
Cation Membrane
Anion Membrane
Dilute (feed water) D Chamber
Dilute (feed water) D Chamber
Dilute (feed water) D Chamber
DOW

R.O Troubleshooting R.O的故障分析

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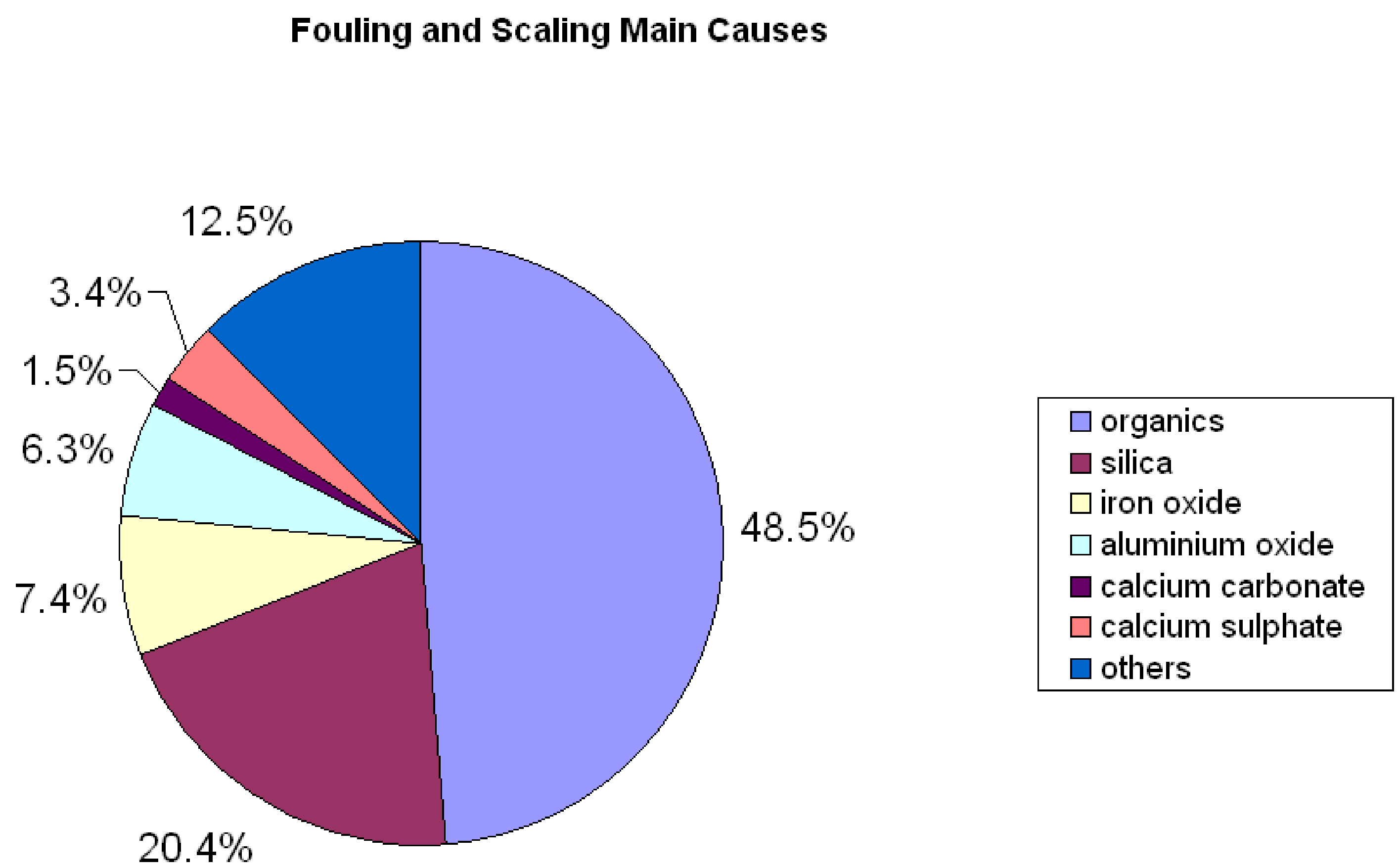

Jane Kucera – NALCO Co.

2006 Int.l Water Conference

Piuttsburg- PA

A practical case of fouling. 污垢的实例

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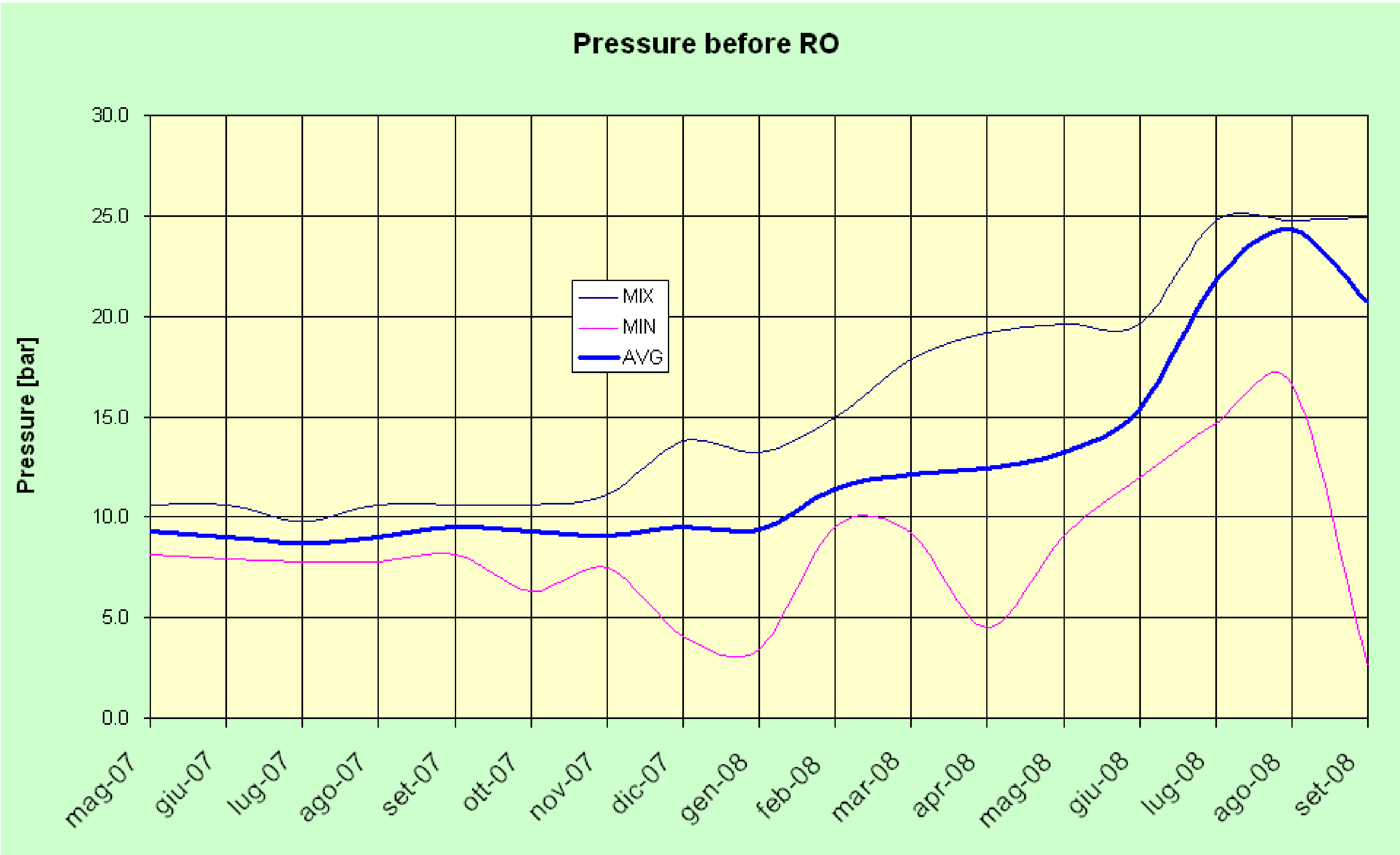
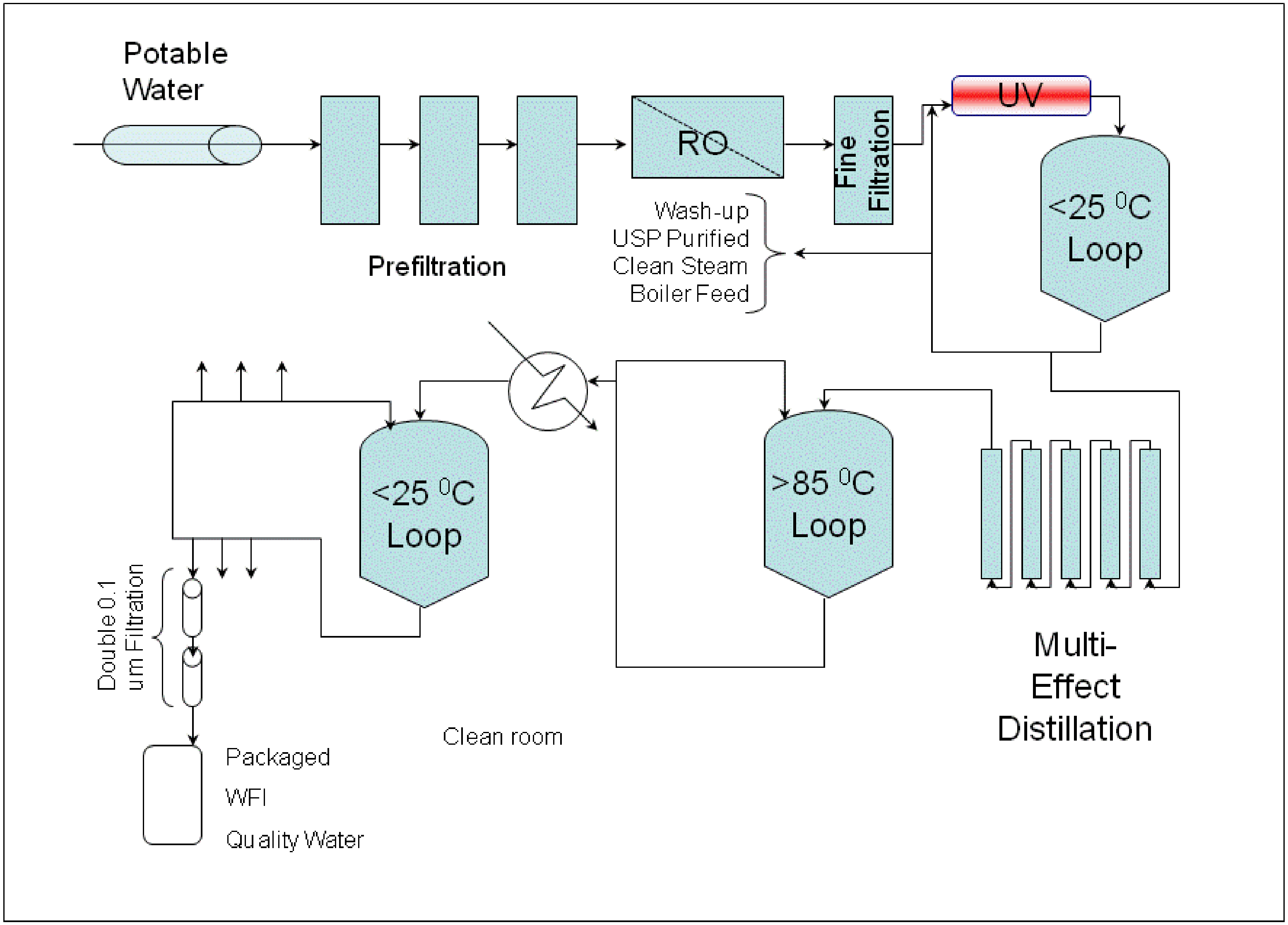
Nevertheless, after the RO membranes, PW was OK 无论如何，通过RO之后，水是合格的。



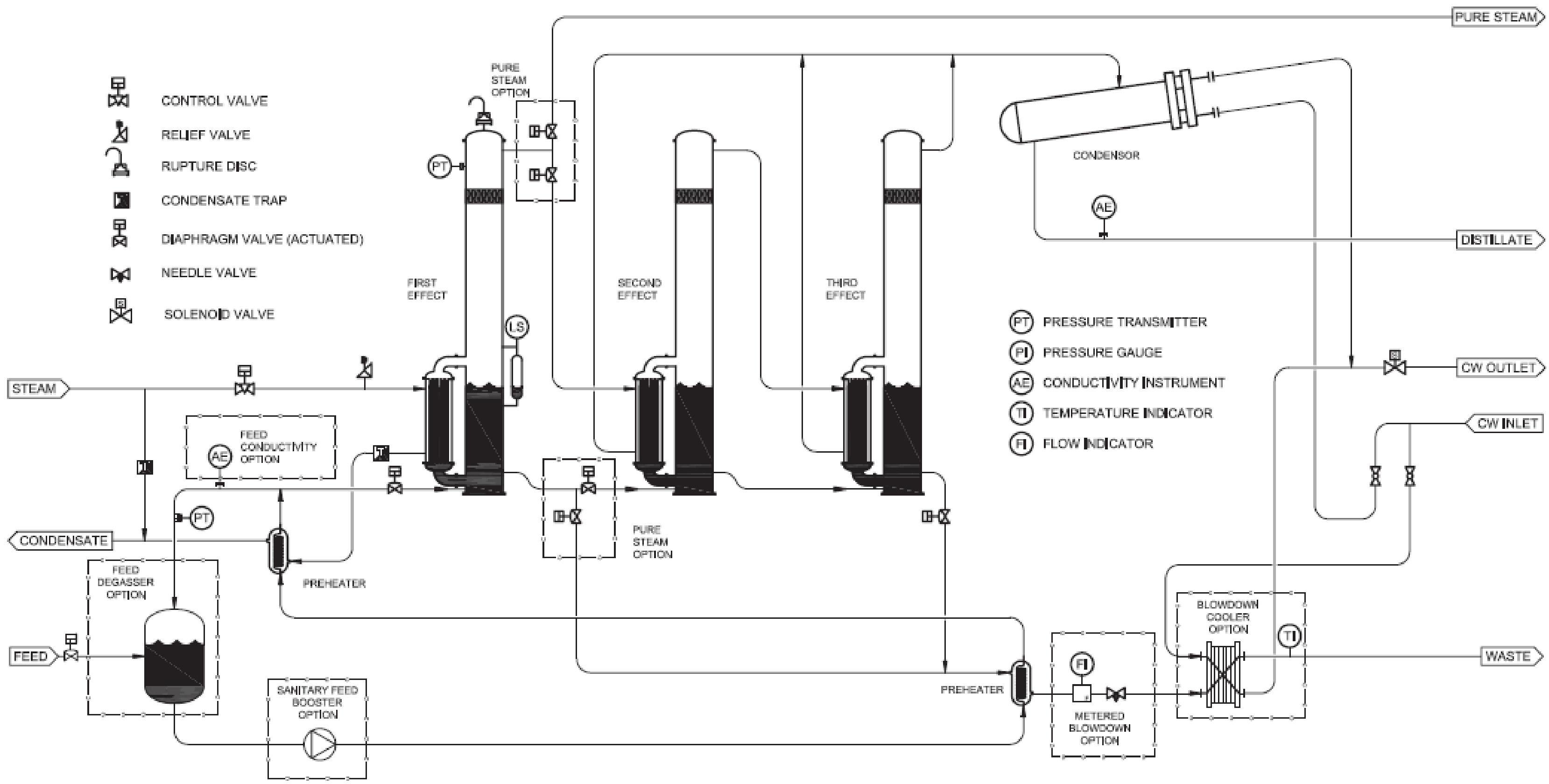
WFI – MULTIPLE EFFECT DISTILLATION

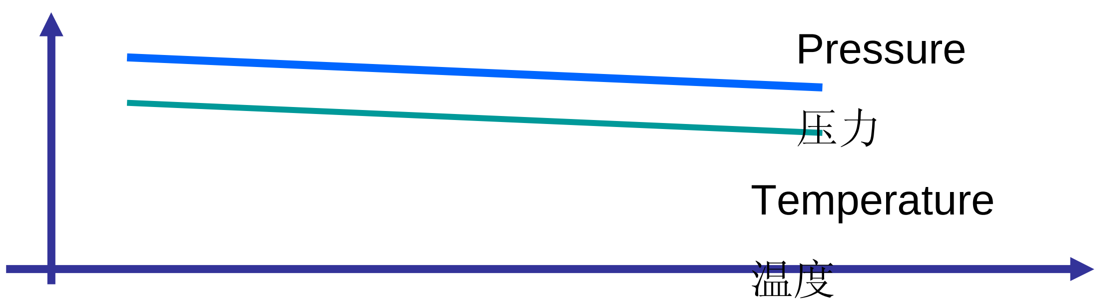
注射用水－多效蒸馏



WFI – MULTIPLE EFFECT DISTILLATION

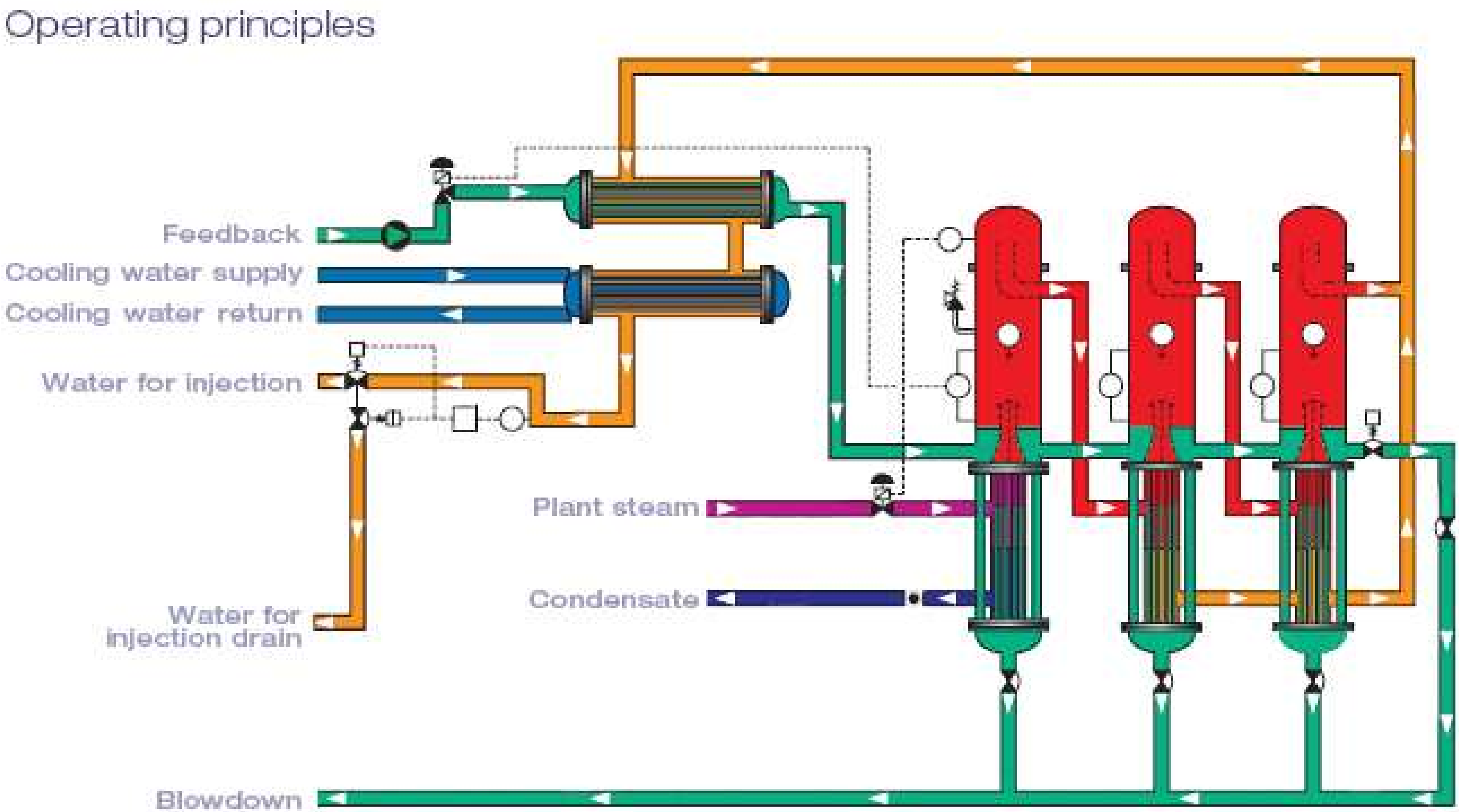
注射用水－多效蒸馏





WFI – MULTIPLE EFFECT DISTILLATION

多效蒸馏

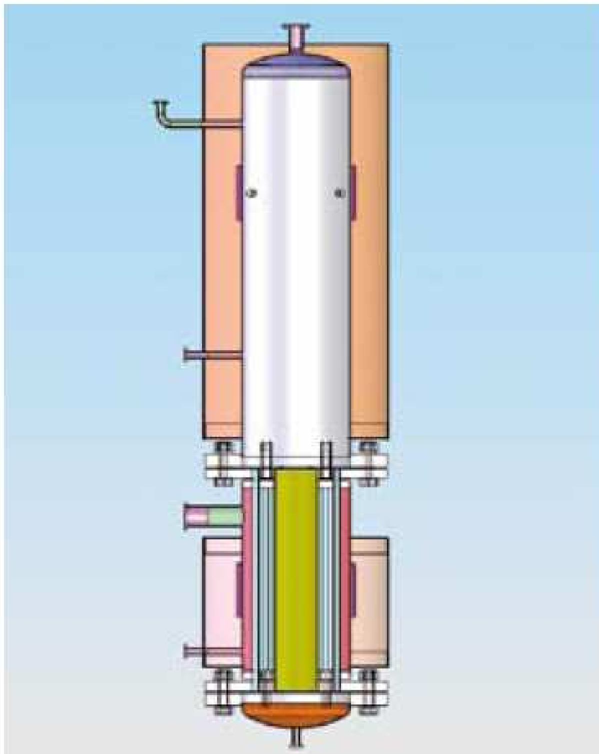


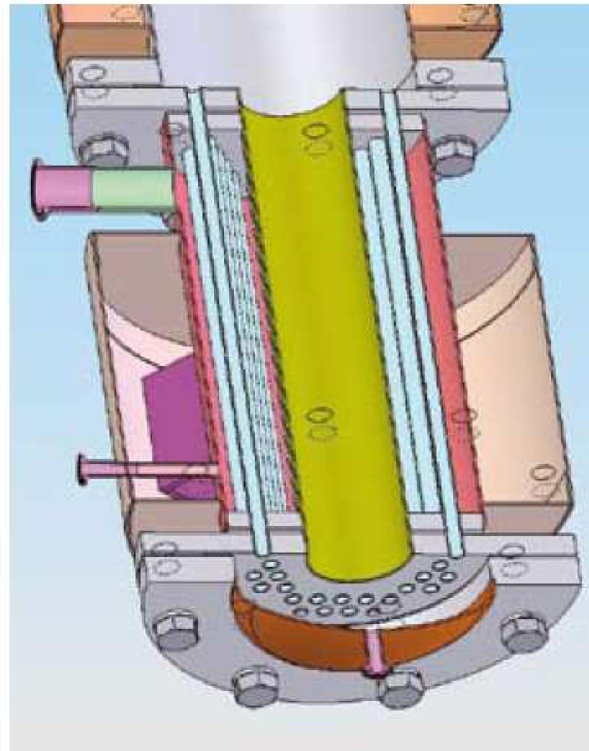
WFI – MULTIPLE EFFECT DISTILLATION

注射用水－多效蒸馏

DISTILLATION COLUMN – EXAMPLE

蒸馏塔－举例





WFI – MULTIPLE EFFECT DISTILLATION

注射用水－多效蒸馏

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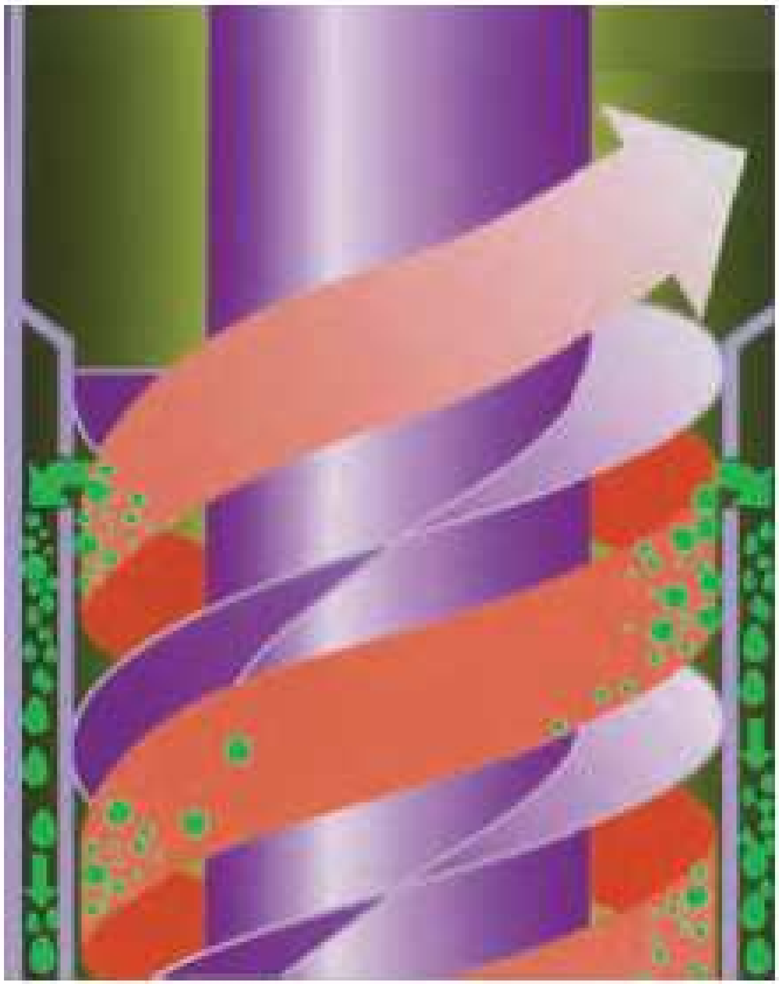
DEMISTER – EXAMPLE

除雾器－举例



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Purified-water system in BHC Beijing Plant
拜耳北京工厂纯化水系统

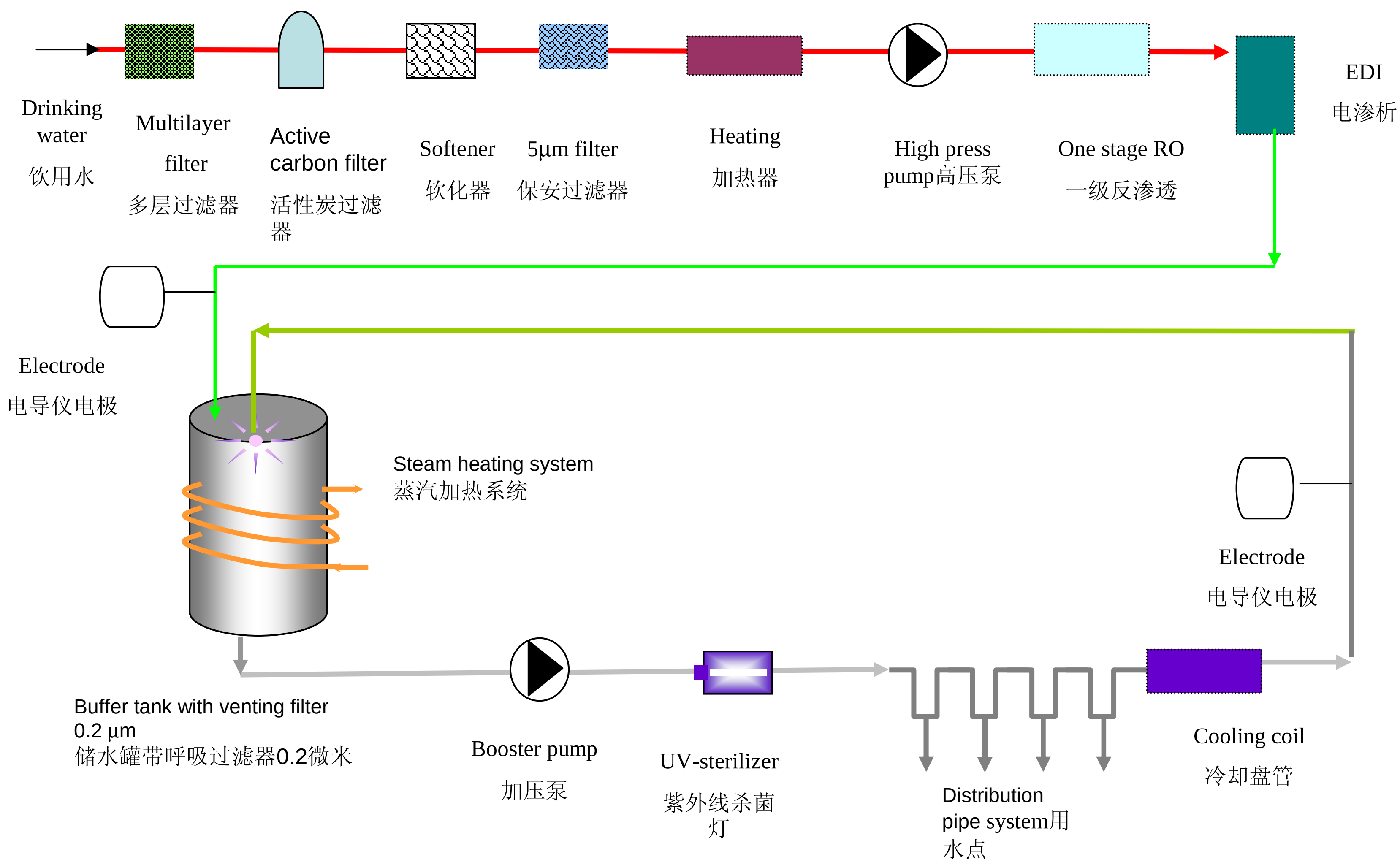
TRAINING SESSION

Specification规格

- **Capacity:** **1.5 m^3/h**
  生产能力 **1.5**吨**/**小时
- **Conductivity:** **< 4.3 μs/cm**
  电导率
- **System:** **1-stage RO＋EDI**
  系统 一级反渗透＋电渗析
- **Storage tank:** **6 m^3**
  储罐 **6**立方米
- **Material AISI 316L (orbital welded)**
- 材料 **316L** （自动氩弧焊）

PW SYSTEM – BEIJING PLANT

System diagram 系统示意图



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Process 制水过程

- Purified Water production纯水制备

System is fed with drinkable water, then raw water passes through multi- layer filter, active carbon filter， water softener, 5 µm particle filter, one-stage RO and finally EDI unit then produces purified water.

系统由饮用水供水，原水经过多层过滤器，活性炭过滤器，软化器，5微米过滤器，一级反渗透膜，最后经过电渗析单元而产出纯化水。

- Purified water storage and circulation纯水的储存和循环

Storage of the process water in a 6 m^3 storage tank with heating jacket

水储存有加热夹套的6 立方米储罐

A booster pump for the feeding and circulation of the purified water, UV light system and heating exchanger in the loop system

循环管路由一台加压泵输送和循环纯化水，并在循环管路中有紫外线杀菌和热交换装置。

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SOP标准操作规程

- S11-001 Operation，Maintenance and usage of Purified water system纯化水系统的操作，维护及使用
- S05-007 Monitoring of purified water system in Beijing plant 北京工厂纯水系统的监测

Sanitation and Monitoring消毒和监测

• Sanitation frequency:	Monthly
• 消毒频率	每月
• Sanitization temperature:	80ºC over 1 hour
• 消毒温度	80度一小时
• Microbiological monitoring:	weekly
• 微生物监测	每周
• Physico-chemical test	weekly
• 理化检测	每周
• Conductivity monitoring:	online
• 电导率监测	在线

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Purified water system 纯化水系统

- Capacity能力: 1.5 m^3/h
- System系统：one stage RO ＋ EDI
- Conductivity电导率: Less than 4.3 µs/cm
- Circulation循环: 6 M^3 buffer tank ＋ booster pump ＋ UV light system ＋ cooling coils
- Sanitization消毒： 80ºC for 1 hour/monthly
- Microbiological monitoring微生物监测: weekly
- Physical & chemical test 理化监测：weekly
- Conductivity monitoring电导率监测：online

Thank you for your attention

Bayer HealthCare

DISCUSSION ON WATER SPEED

水流速的讨论

BACKUP
备用 1

Università degli Studi di Bologna

Facoltà di Ingegneria

Corso di Laurea in Ingegneria Meccanica

Dipartimento di Ingegneria delle Costruzioni Meccaniche, Nucleari, Aeronautiche e di Metallurgia

Impianti Industriali e Meccanici

IMPIANTO DI PRODUZIONE PER ACQUA FARMACEUTICA

Tesi di Laurea di:

Mirko SBARAGLIA

Relatore:

Chiar.mo Prof. Ing. Cesare SACCANI

Correlatori:

Ing. Michele COCIANI

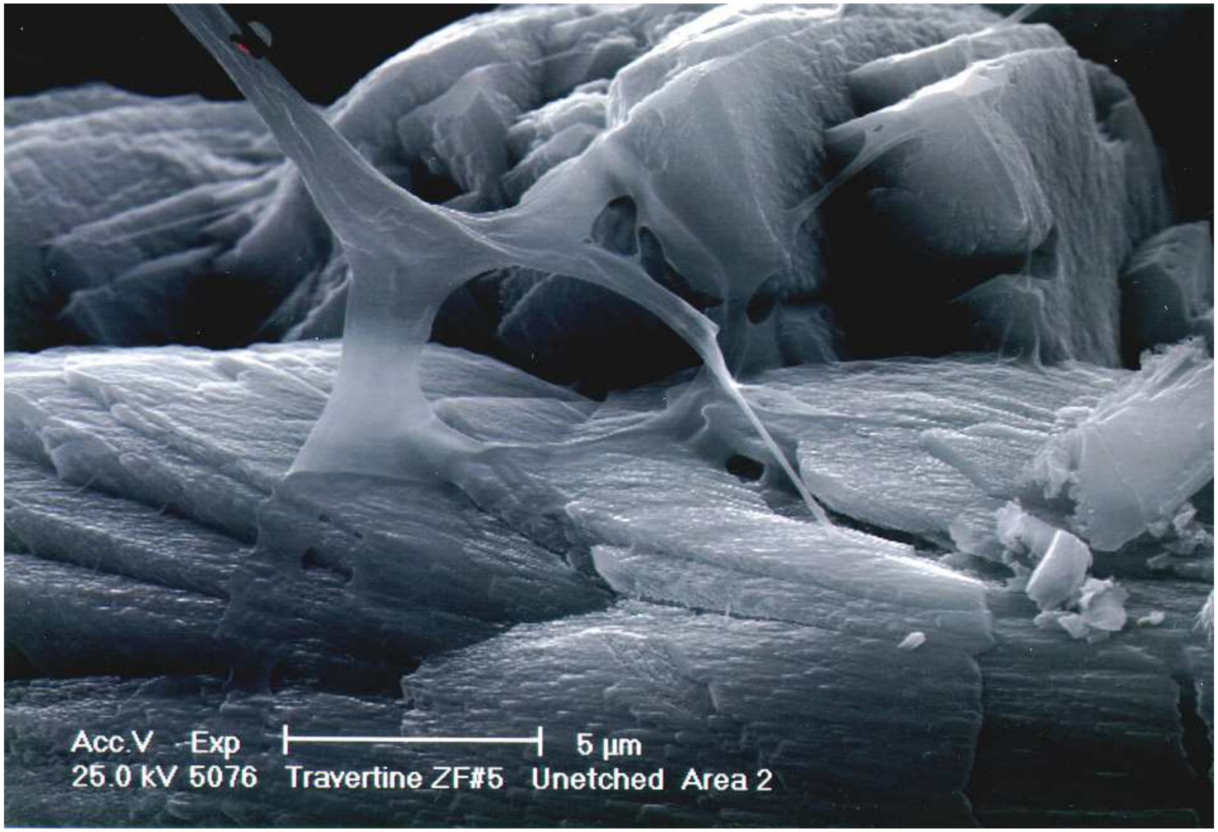
Ing. Augusto BIANCHINI

Anno Accademico 2002-2003

Biofilm 生物膜

DEF: ***The Biofilm is a well structured matrix of bacterial populations bonded with each other and with a solid interface***

定义：生物膜是在固体表面由细菌群形成的集合体。



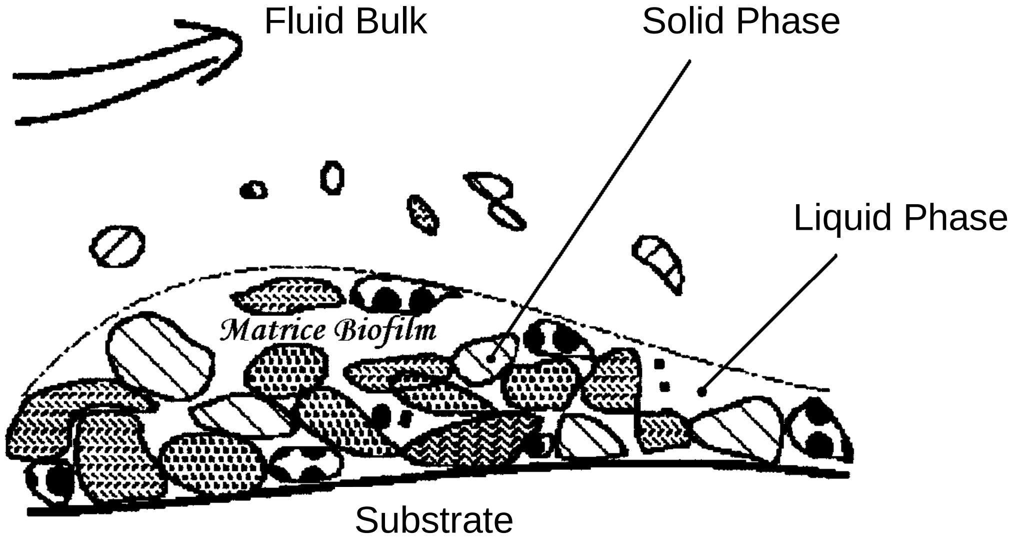
Scope of Thesis 范围

- Analysis of a PW distribution system trough suitable mathematical modelling for motion and biofilm growth (bacteria) 通过合适的数学模型来分析纯水分配系统的运动和生物膜的生长。

- Fluid motion simulation inside pipes to find possible critical points regarding biofilm growth 通过模拟管内流体的运动来找出生物膜生长的关键点。

Mathematical Model 数学模型

- ***Fluid Bulk 流体***
- ***<u>Biofilm</u> 生物膜***
  - a) ***Liquid Phase 液态相***
  - b) ***Solid Phase 固态相***
- ***<u>Substrate 底层</u>***



PDEs

Fluid Bulk 流体

1) **Continuity**

$$\nabla \cdot \bar{u} = 0$$

2) **Navier-Stokes**

$$\frac{\partial \bar{u}}{\partial t} + \bar{u} \cdot grad \cdot \bar{u} - \nu \cdot \nabla^2 \bar{u} + \nabla \bar{P} + \left[\nabla \cdot \bar{\tau}^l \right] + \left[\nabla \cdot \bar{\tau}^t \right] = \bar{F}$$

3) **Mass Balance**

$$\frac{\partial C_i}{\partial t} + u \cdot \nabla C_i = \nabla \cdot \left(D_i \left(X \right) \cdot \nabla C_i \right) + r_i \qquad i = 1, \dots, n_l$$

$$\nabla = \frac{\partial}{\partial x} \hat{i} + \frac{\partial}{\partial y} j + \frac{\partial}{\partial z} \hat{k}$$

$$\nabla^2 = \frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2}$$

Biofilm 生物膜

1) **Volume fraction**

$$\sum_k \varepsilon_k = \varepsilon_l + \sum_s \varepsilon_s = 1$$

2) **Mass Balance for Dissolved Species**

$$\frac{\partial \varepsilon_l C_{l,i}}{\partial t} = -\nabla \left(-D_{l,i} \left(X \right) \nabla C_{l,i} \right) + r_{l,i} \qquad i = 1, \dots, N_s$$

3) **Growth Equation for Biofilm**

$$\frac{dL_f \left(\zeta, t \right)}{dt} = \frac{1}{\rho_s \cdot \varepsilon_s} \int_0^{L_f} r_s d\zeta + \frac{f}{\varepsilon_s \cdot \rho_s}$$

4) **Growth Kinetics (Monod Type)**

$$r_s = \mu_{\max} \frac{\rho_s \cdot C_{l,i}}{K + C_{l,i}} - b \cdot \rho_s$$

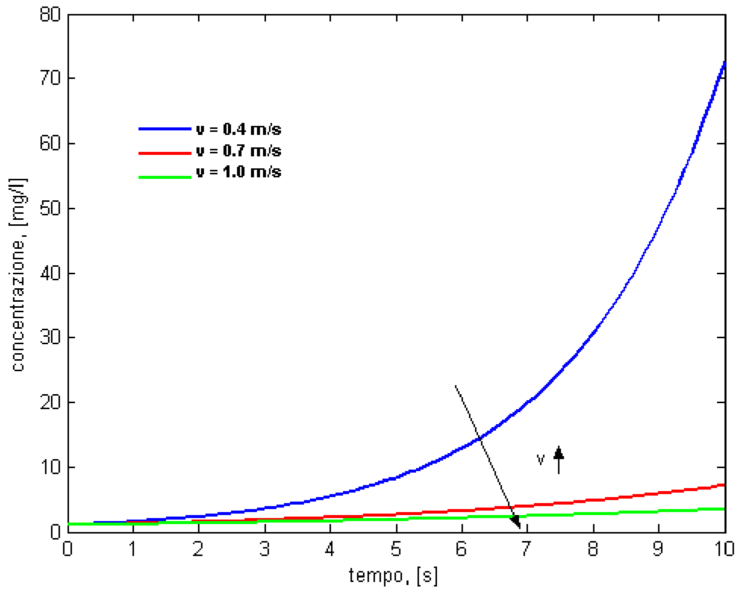
$$r_{l,i} = \frac{\mu_{\max}}{Y} \cdot \frac{\rho_s \cdot C_{l,i}}{K + C_{l,i}}$$

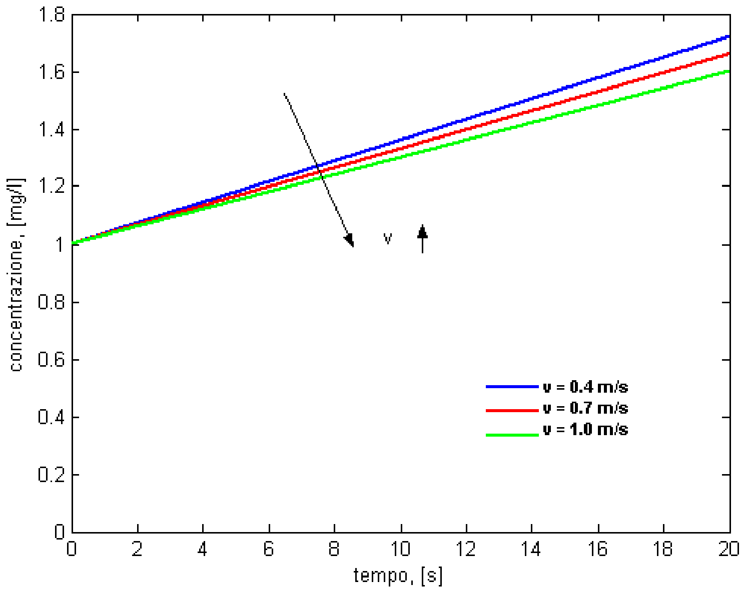
Growth Dynamic 动态生长

Due to math reasons (solution in implicit forms) the representation is given in two domains. 在数学层面上， 用两部分来标示。

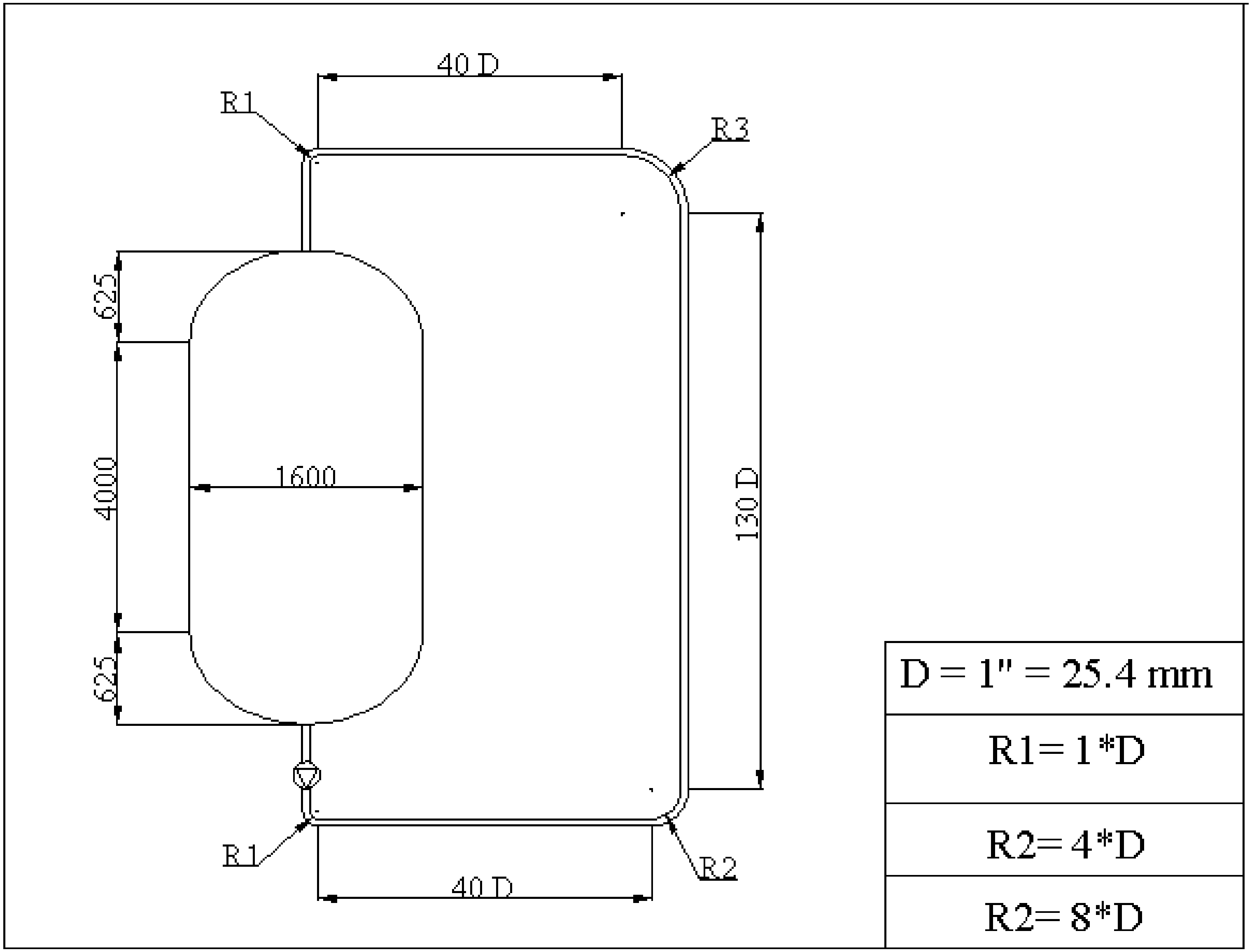
→Biofilm Growth Diminish Nonlinearly With PW Speed

→生物膜的减少与水流速是非线性关系





Model 模型



40 D
R1
R3
625
4000
1600
130 D
625
R1
R2
40 D
D = 1" = 25.4 mm
R1= 1*D
R2= 4*D
R2= 8*D

Simulation 仿真

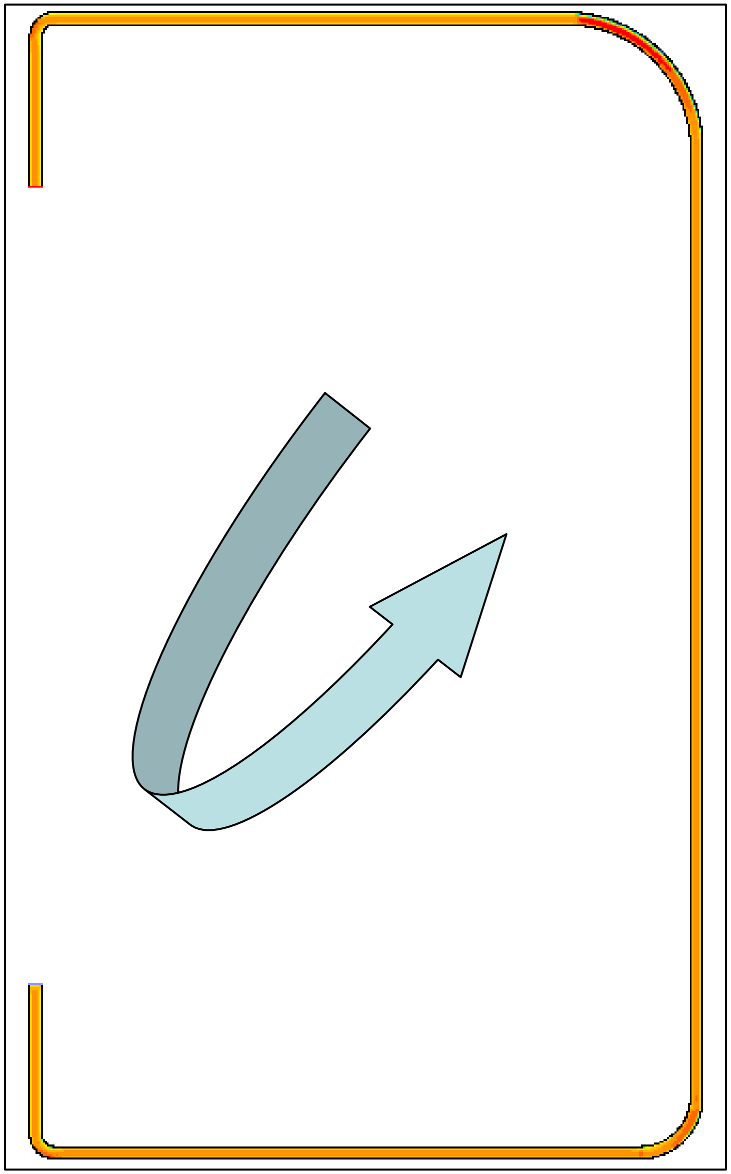
Results from FLUENT release 5.5 结果

▪ V	0.4 m/s	
▪Ra	0	μm

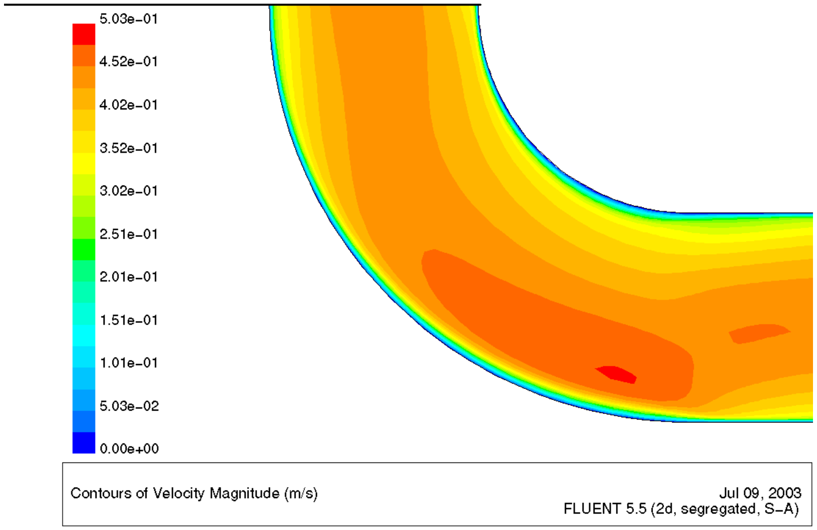
▪ V	0.6 m/s	
▪Ra	0	μm

▪ V	0.8 m/s	
▪Ra	0	μm

▪ V	1.0 m/s	
▪Ra	0	μm



V = 0.4 m/s Ra = 0 μm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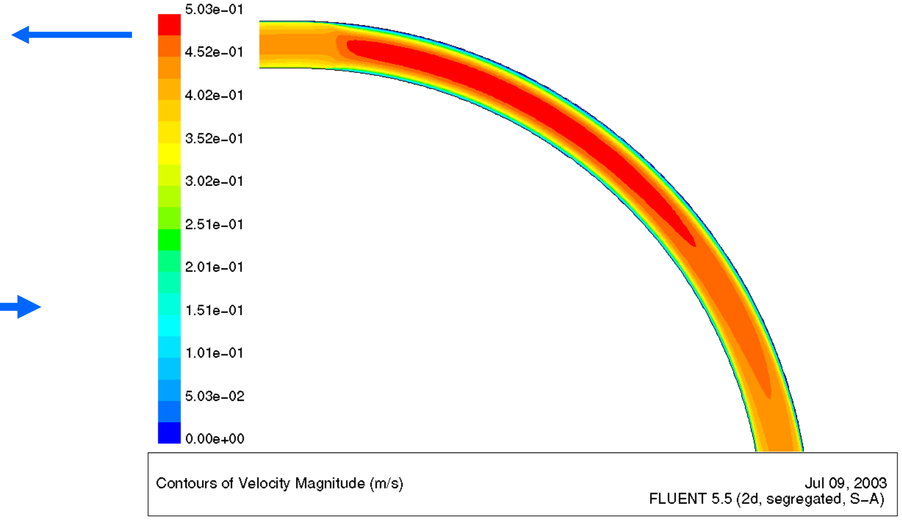
4.02e-01
3.52e-01
3.02e-01
2.51e-01
2.01e-01
1.51e-01
1.01e-01
5.03e-02
0.00e+00
Contours of Velocity Magnitude (m/s)
Jul 09, 2003
FLUENT 5.5 (2d, segregated, S-A)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0.00e+00
Contours of Velocity Magnitude (m/s)
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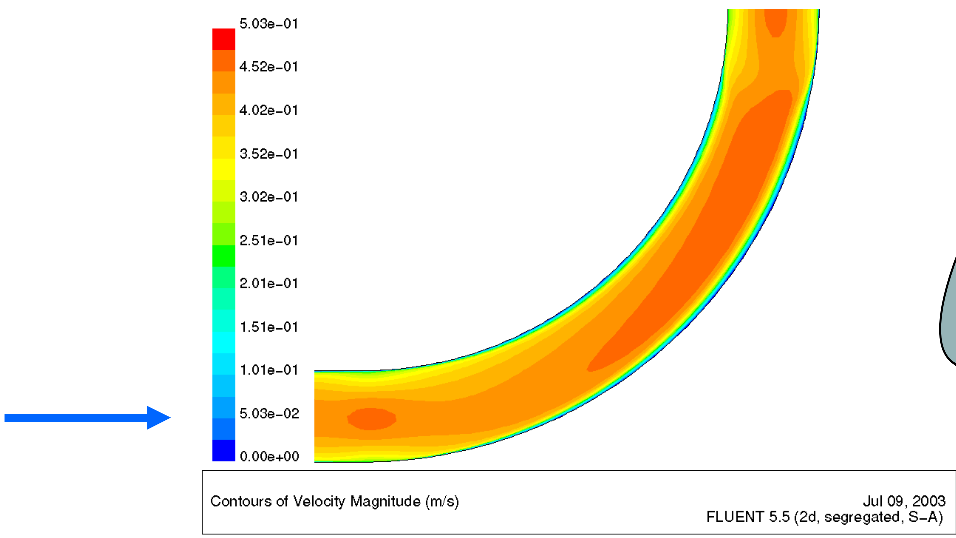
FLUENT 5.5 (2d, segregated, S-A)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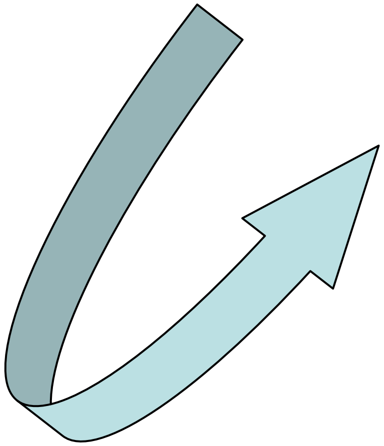
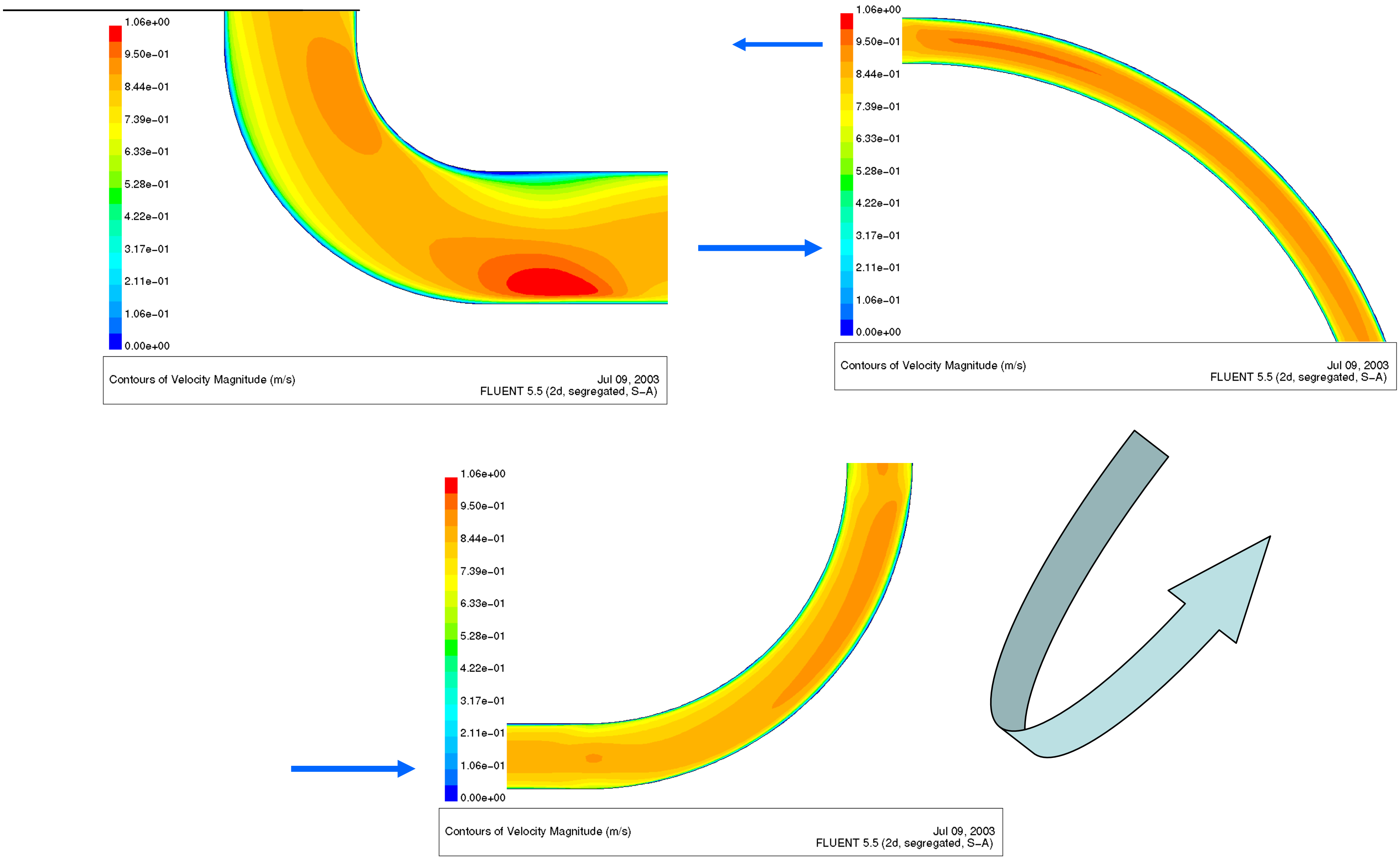
0.00e+00
Contours of Velocity Magnitude (m/s)
Jul 09, 2003
FLUENT 5.5 (2d, segregated, S-A)



V = 0.8 m/s Ra = 0 μm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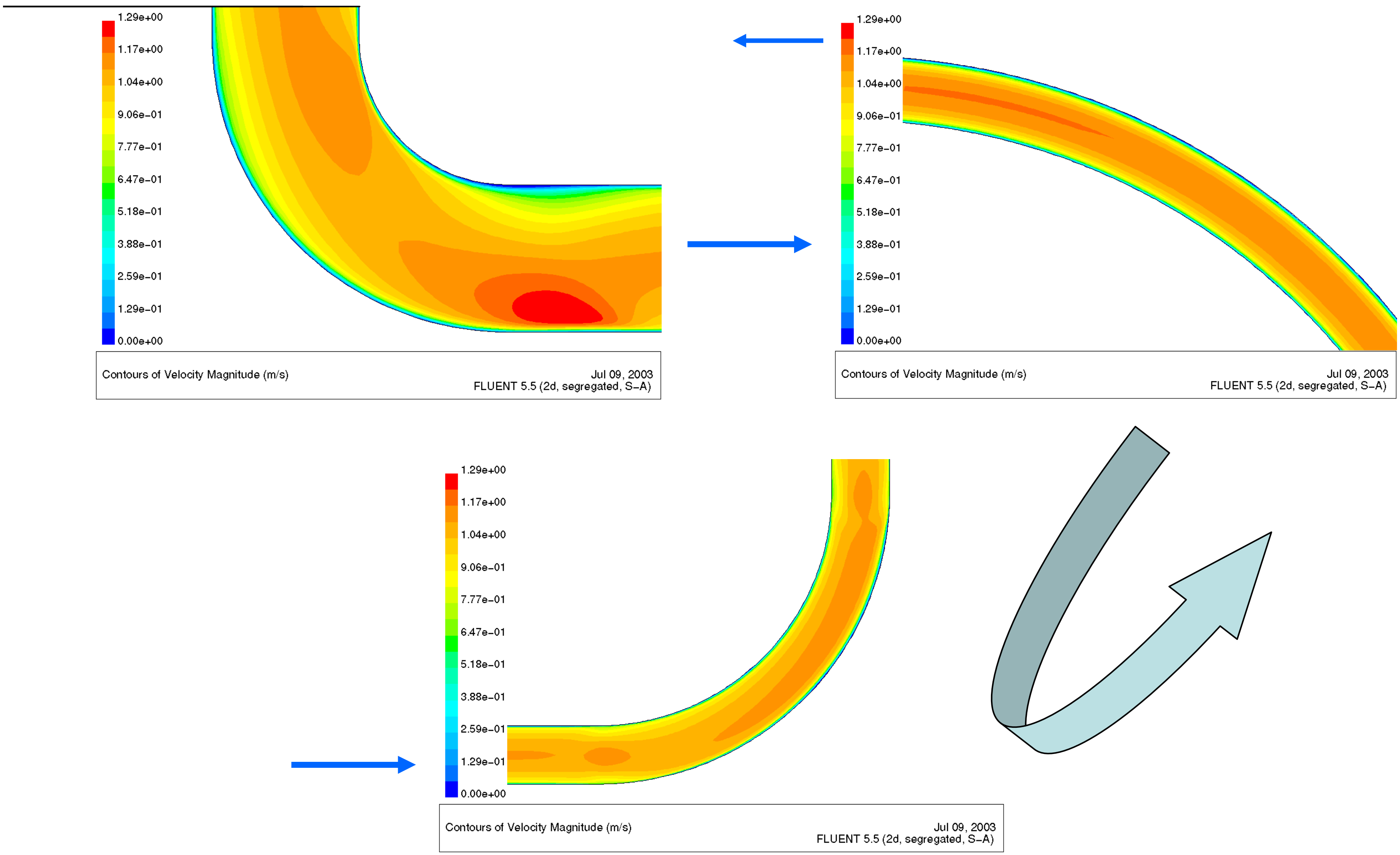
9.50e-01
8.44e-01
7.39e-01
6.33e-01
5.28e-01
4.22e-01
3.17e-01
2.11e-01
1.06e-01
0.00e+00
Contours of Velocity Magnitude (m/s)
Jul 09, 2003
FLUENT 5.5 (2d, segregated, S-A)
1.06e+00
9.50e-01
8.44e-01
7.39e-01
6.33e-01
5.28e-01
4.22e-01
3.17e-01
2.11e-01
1.06e-01
0.00e+00
Contours of Velocity Magnitude (m/s)
Jul 09, 2003
FLUENT 5.5 (2d, segregated, S-A)
1.06e+00
9.50e-01
8.44e-01
7.39e-01
6.33e-01
5.28e-01
4.22e-01
3.17e-01
2.11e-01
1.06e-01
0.00e+00
Contours of Velocity Magnitude (m/s)
Jul 09, 2003
FLUENT 5.5 (2d, segregated, S-A)

v = 1.0 m/s Ra = 0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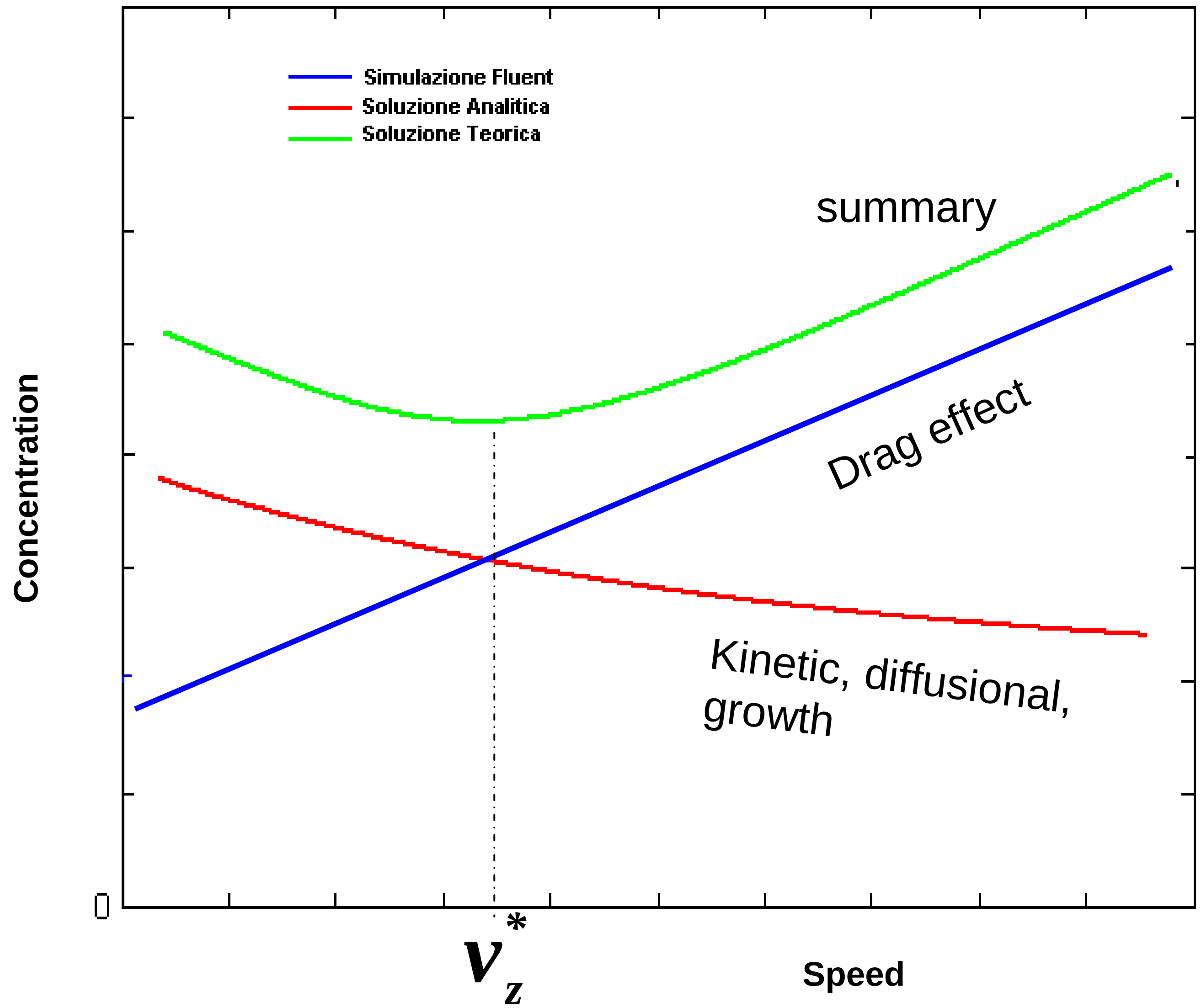
7.77e-01
6.47e-01
5.18e-01
3.88e-01
2.59e-01
1.29e-01
0.00e+00
Contours of Velocity Magnitude (m/s)
Jul 09, 2003
FLUENT 5.5 (2d, segregated, S-A)
1.29e+00
1.17e+00
1.04e+00
9.06e-01
7.77e-01
6.47e-01
5.18e-01
3.88e-01
2.59e-01
1.29e-01
0.00e+00
Contours of Velocity Magnitude (m/s)
Jul 09, 2003
FLUENT 5.5 (2d, segregated, S-A)
1.29e+00
1.17e+00
1.04e+00
9.06e-01
7.77e-01
6.47e-01
5.18e-01
3.88e-01
2.59e-01
1.29e-01
0.00e+00
Contours of Velocity Magnitude (m/s)
Jul 09, 2003
FLUENT 5.5 (2d, segregated, S-A)

Result 结果



Simulazione Fluent
Soluzione Analitica
Soluzione Teorica
summary
Drag effect
Kinetic, diffusional, growth
Concentration
0
v_z^*
Speed

PRE TREATMENT IN BHC GARBAGNATE PLANT

BACKUP 2

Purified Water Plant – pre treatment: Ion Exchanger
纯水－预处理：离子交换器