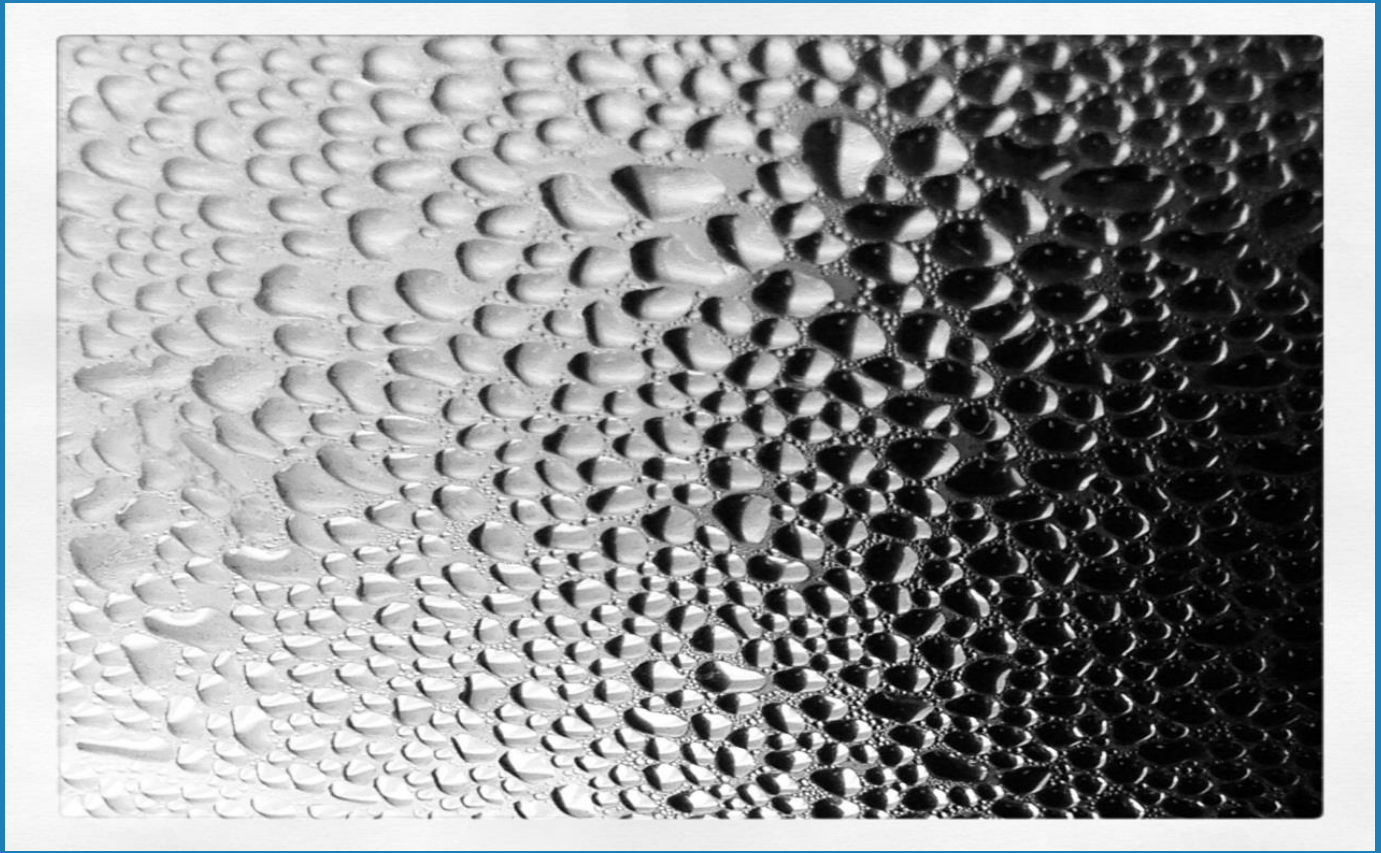
GMP WORKSHOP

WATER for Pharmaceutical Use



DCVMN WORKSHOP - Victor Maqueda - May 30, 31, June 1 2016

Learning objectives

- At the end of this module, the participant should be able to identify critical points in Water Systems in order to improve GMP compliance and be better prepared to face regulatory inspections.

Outline

- Water System and Pure Steam (principles and requirements)
- Design
- Installation
- Validation
- Points to consider
- Exercises
- References

Water for pharmaceutical use (WPU)

Principles

- It is more than just a utility. It is like producing a starting material.
- It is like the blood of the facility.
- Designed to prevent/control microbial growth (Biofilm), pyrogens or endotoxins, and particles.
- Shall meet pharmacopeia microbial and physicochemical specifications

Water for pharmaceutical use

Why purify raw water?

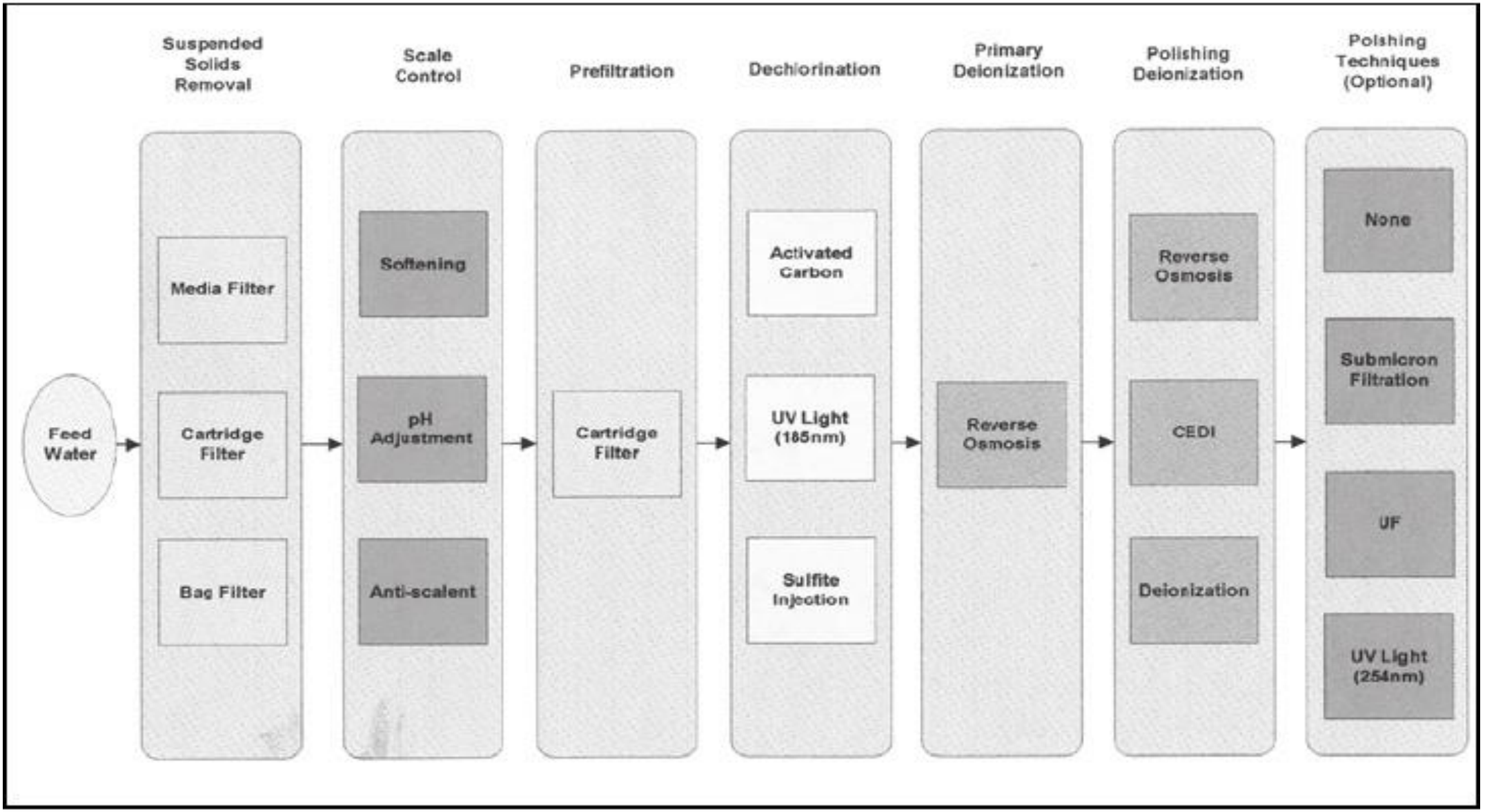
- May be variable due to seasonal variations, regional variation in water quality.
- Must remove impurities and control microbes, chlorine (if City Water).
- Design and purification treatment depends on raw water's chemistry and contaminants, influenced by, e.g. rainfall, erosion, pollution, dissolution, sedimentation, decomposition.

Water for pharmaceutical use

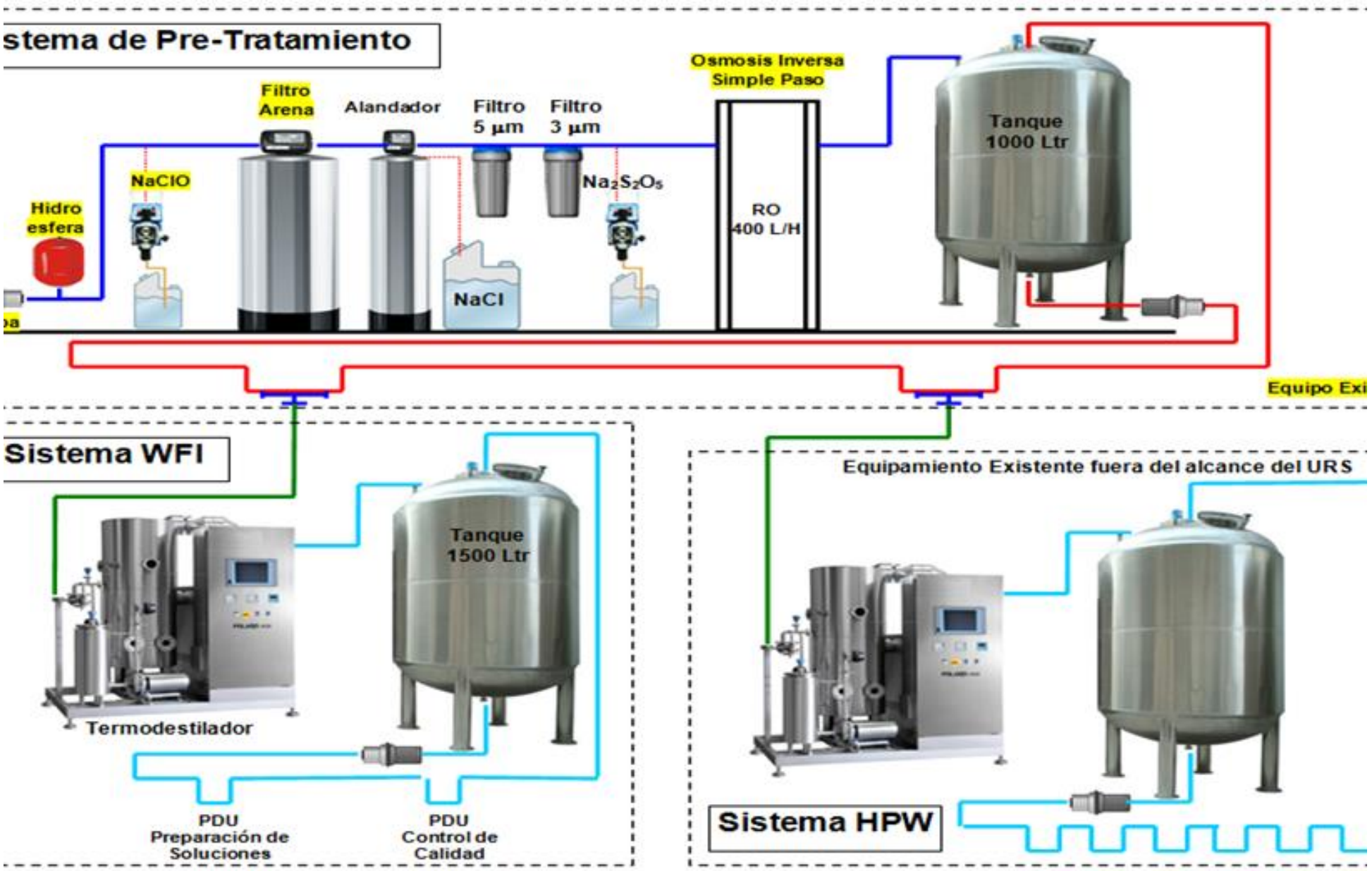
Water system requirements

- Design, installation, commissioning, qualification / validation, operation, performance and maintenance to ensure reliable, consistent production of water of required quality
- Operate within design capacity
- Prevent unacceptable microbial, chemical and physical contamination during **production, storage and distribution**
- Quality Assurance involved in approval of use after installation and maintenance work

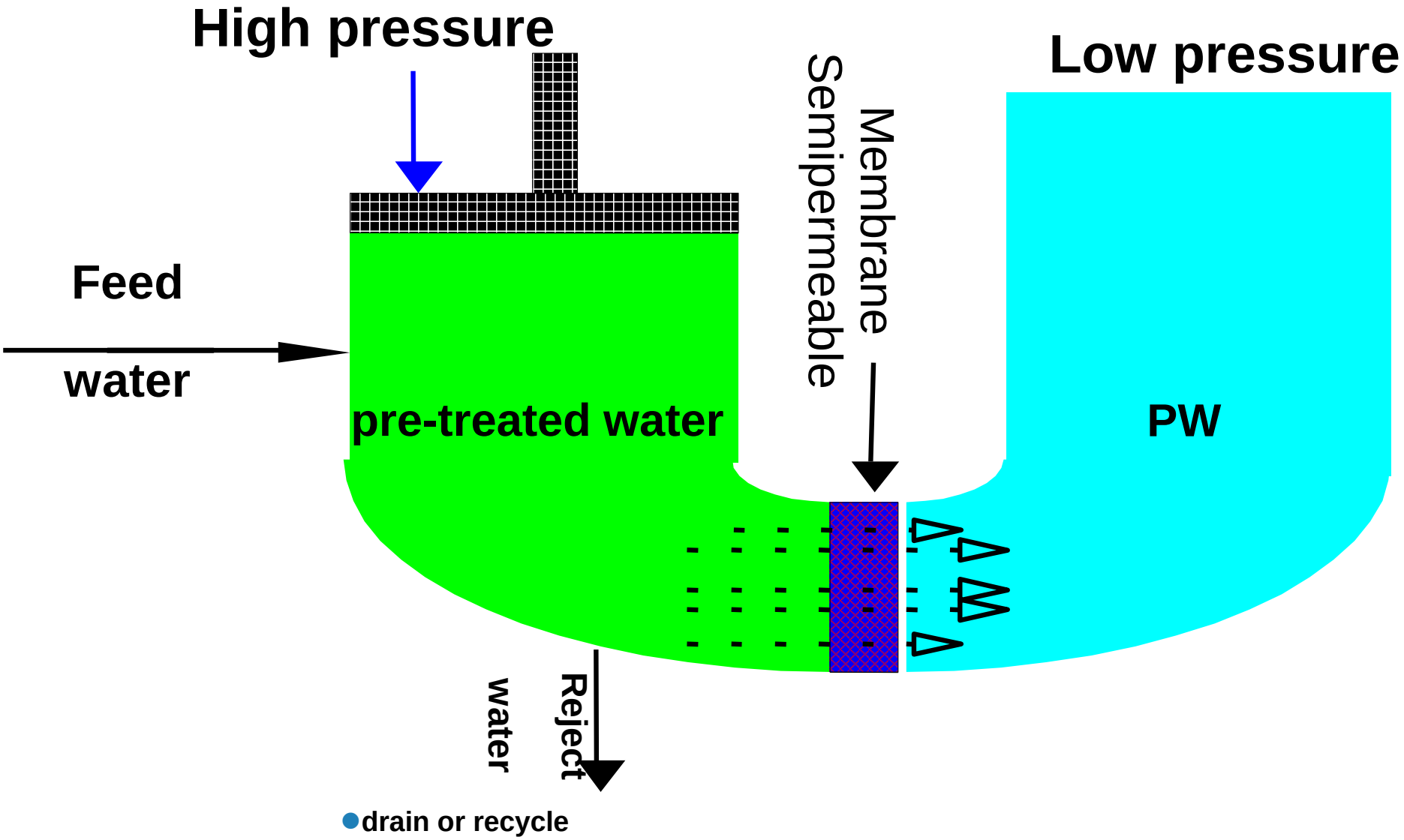
BASIC STAGES IN WPU PRODUCTION

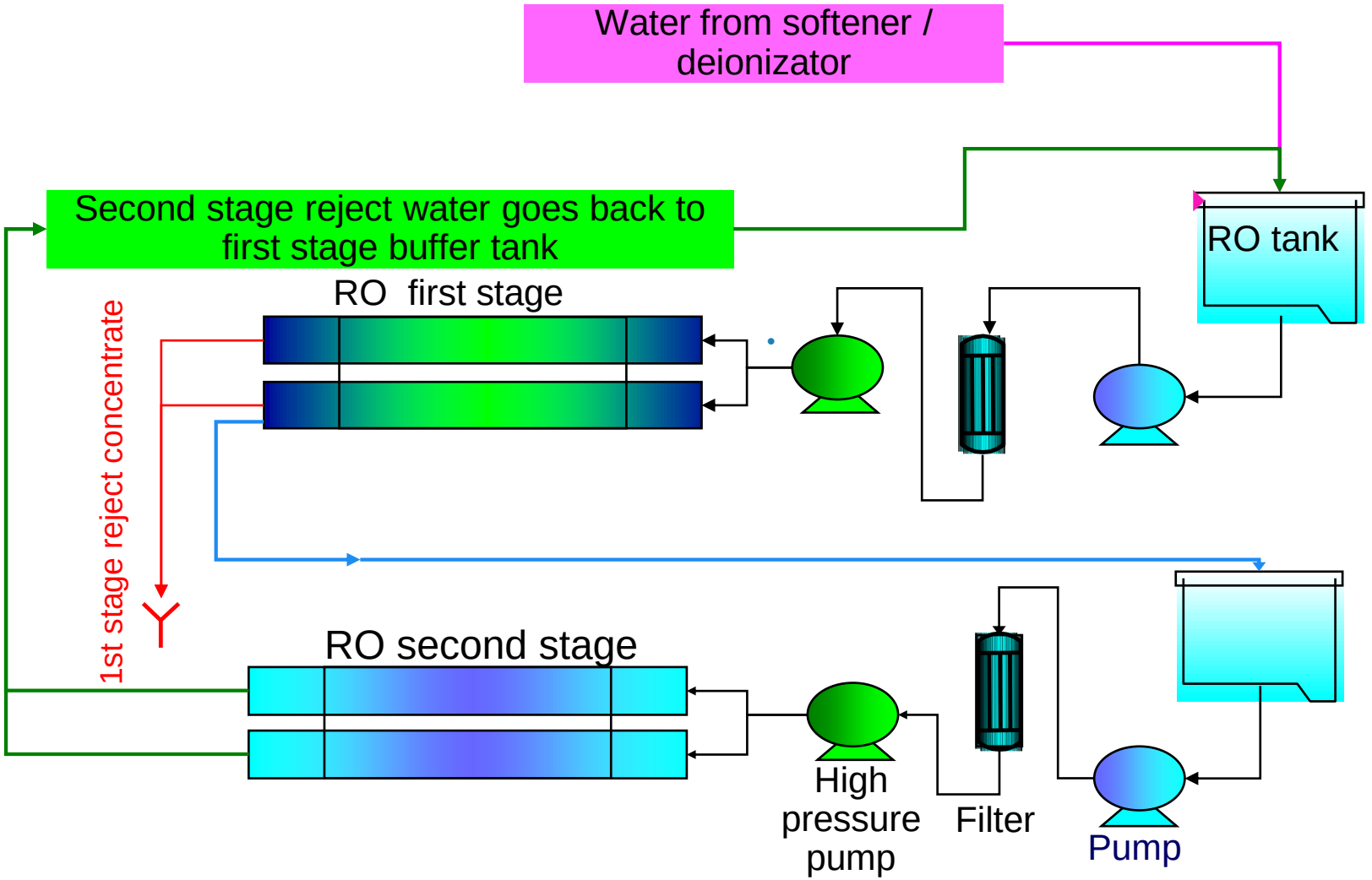


Diseño general típico / Typical WPU Design



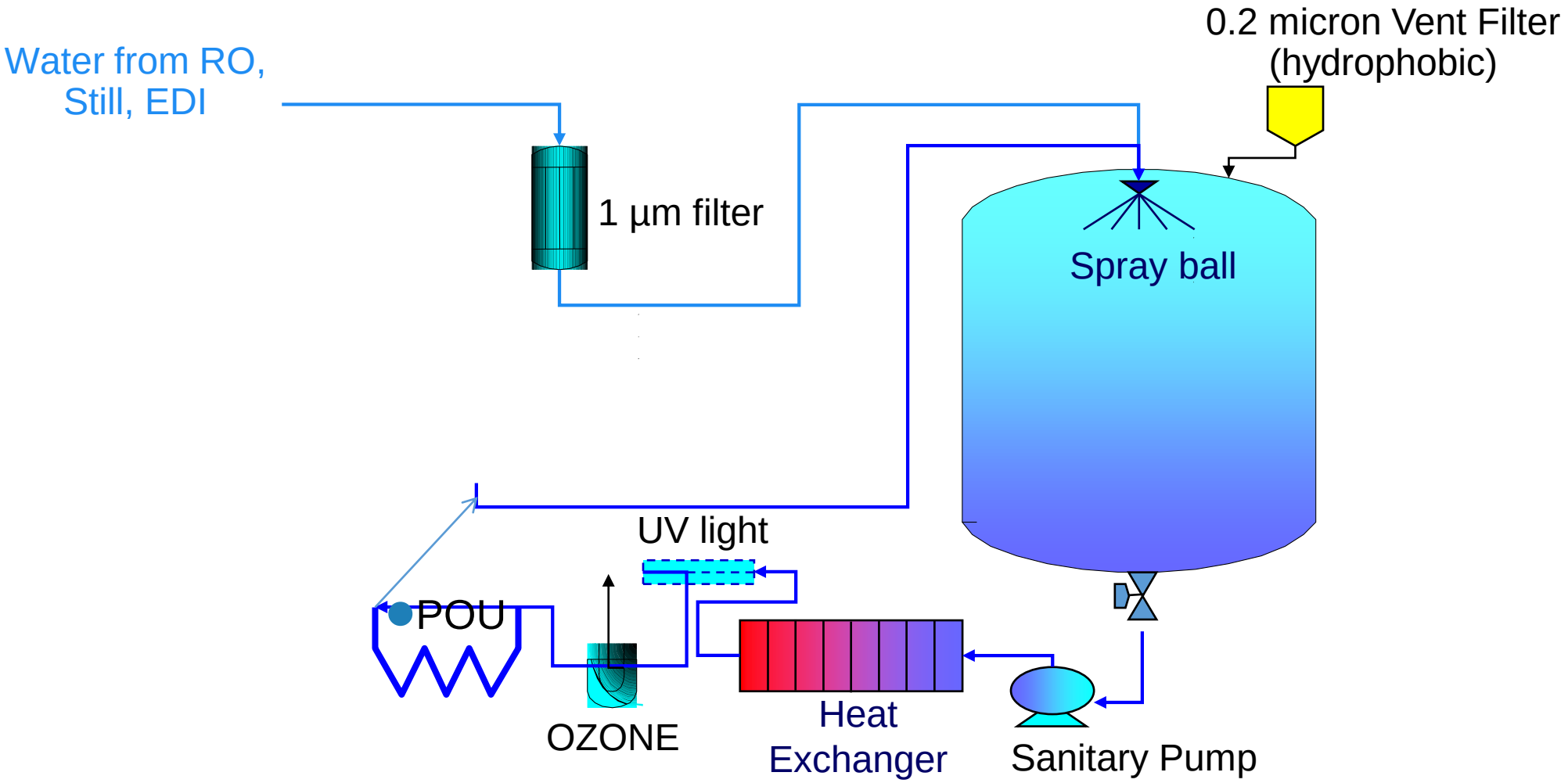
Reverse Osmosis (RO)





Double pass Reverse Osmosis system

WFI / PW Storage & Distribution



Water for pharmaceutical use

Water system requirements

- Monitoring of water sources regularly
  - *Chemical and microbiological*
  - *Endotoxin level where relevant (eg. WFI)*
- Monitoring of system performance, storage and distribution.
- Records of results, and action taken.
- Validated sanitization procedure followed on a routine basis.

WATER SYSTEM PROJECT

“Practical guidelines for qualifying purified water systems”

or Water for Pharmaceutical Use (WPU)

- Purified water (PW) or Water for Injection (WFI) as a raw material or for cleaning equipment.

- The typical qualification sequence DQ-IQ-OQ-PQ

- During routine, need intensive monitoring and regular inspections.

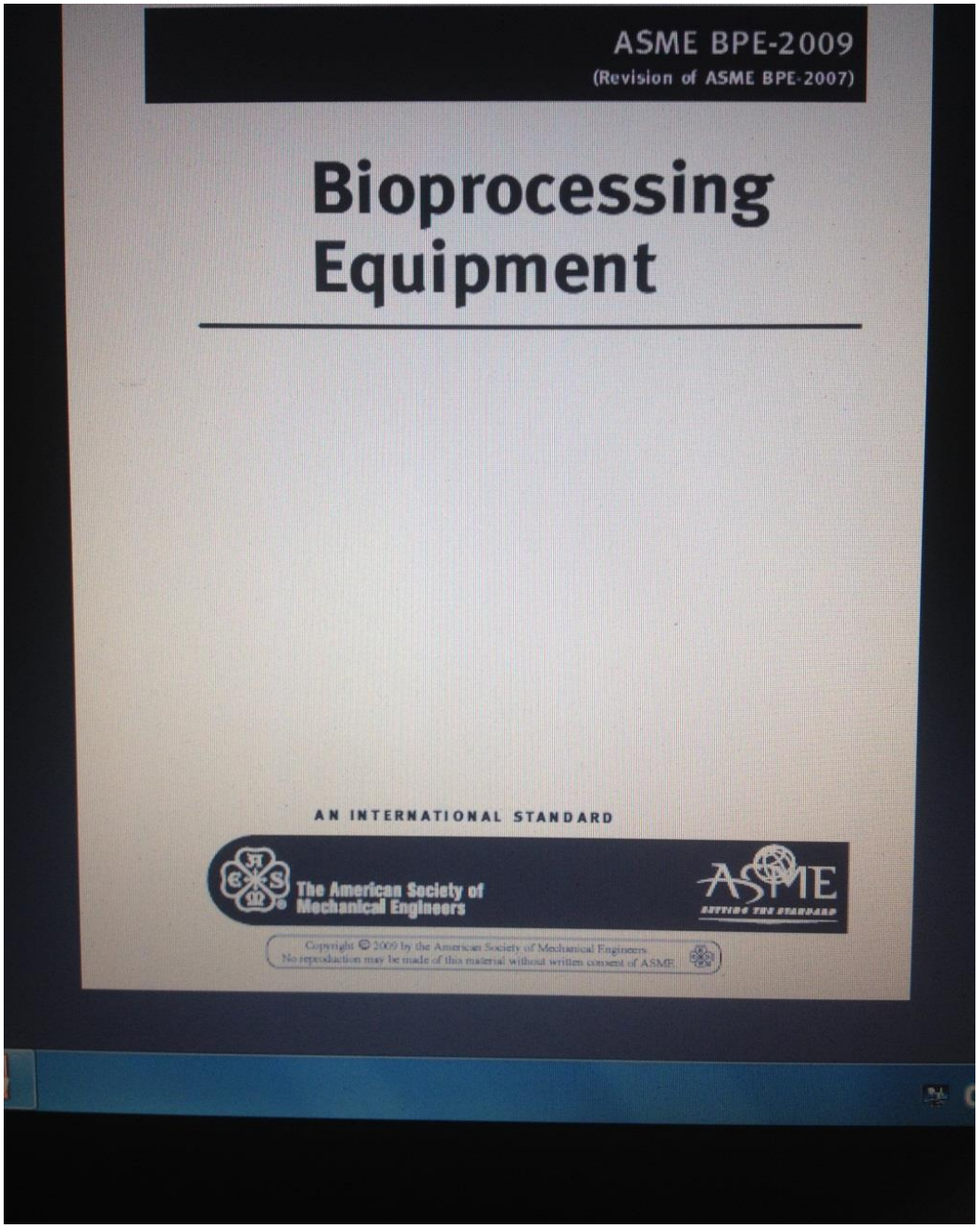
Quality and Project Plan (QPP)

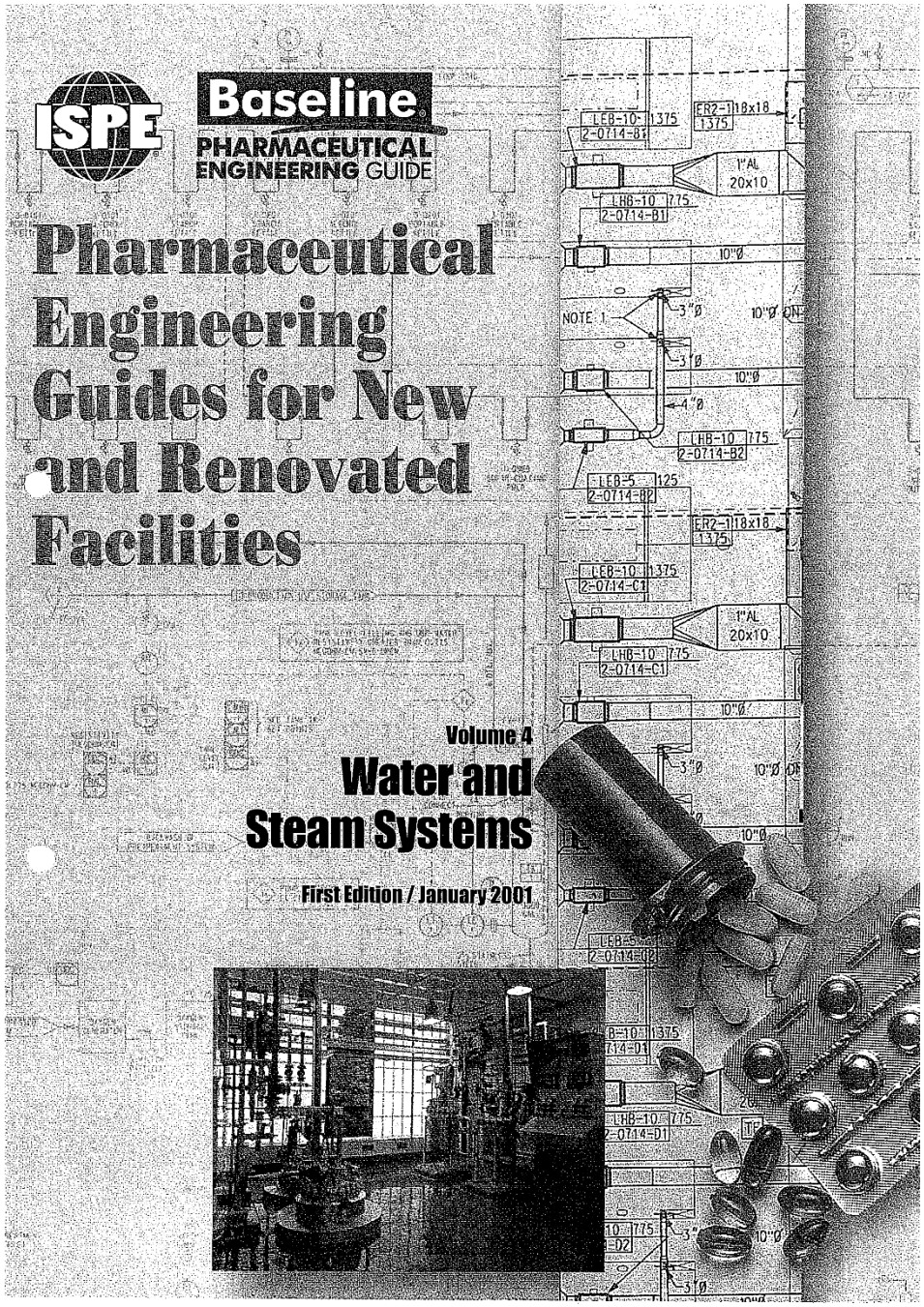
- QPP is prepared at the beginning of the project. Includes:
  - Who is the project leader and how planning will be carried out
  - How communication and coordination is performed between departments and with external contractors.
  - How the information will be delivered to the project manager.
  - Exceptions to the agreed protocols.
  - Document (design, protocols, reports) approval process.
  - Responsibles for reviewing and approving the types of documents.
  - Number of days assigned to the review process.
  - In which form comments must be returned. How to manage changes.

Requirements for PW installations

- Pharmacopoeias (e.g., USP, EP, JP).
- cGMP, 21 Code of Federal Regulations., WHO, PICs
- National laws and regulations.
- Engineering standards (eg. American Society of Mechanical Engineers—ASME)

Reference: ASME BPE




ISPE
Baseline
PHARMACEUTICAL
ENGINEERING GUIDE
Pharmaceutical Engineering Guides for New and Renovated Facilities
Volume 4
Water and Steam Systems
First Edition / January 2001

USER's REQUIREMENTS SPECIFICATIONS (URS)

- URS should be clear, well-structured, numbered and testable (eg. avoid "heat exchangers must be of a high quality…')
- Temperature, hardness, plant/QC operators safety.
- A risk analysis regarding the end product (e.g., water quality) should be performed before compiling the URS.
- Divide the URS into 'C' and 'Q' requirements based on the risk analysis performed (ISPE).
  - C: stands for Commissioning and the requirement will then be tested under a factory acceptance test (FAT) or a site acceptance test (SAT).
  - Q: stands for Qualification and the requirement is tested under an installation qualification (IQ) or an operation qualification (OQ).
- To facilitate traceability in the project, write the requirement specification in table format which then the supplier can use to create a traceability matrix.

USER's REQUIREMENTS SPECIFICATIONS (URS)

- Crucial to have an analysis of the incoming water to design the system correctly with the right pretreatment for the application.
- How much water will I need for manufacturing, cleaning, Pure Steam production, etc ?
- Consider simultaneous usage !
- Points of use (POU) and Sample points

USER's REQUIREMENTS SPECIFICATIONS (URS)

- Materials of Construction (MOC)
- Instrumentation
- Data Acquisition & Management systems
- Temperature – Sanitization – Drainability
- Alarms

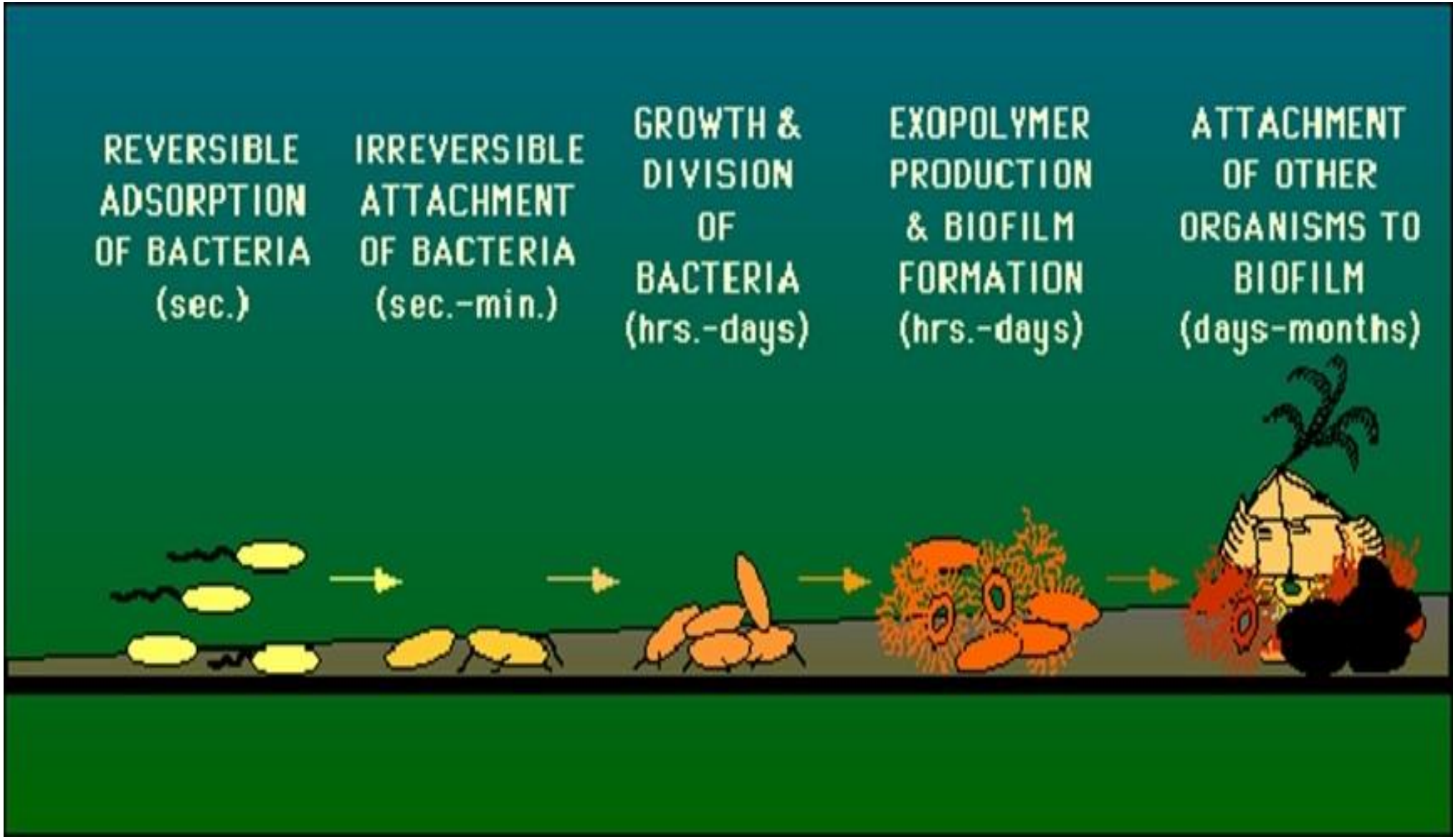
Example 1 of URS: General design features

- WFI-PS generator shall produce 800 #/hr of pure steam and 25 gph of WFI as defined by the current United States Pharmacopoeia (USP).
- The WFI system will store and circulate water at 80°C from a 400 gallon SS316L storage tank and through SS316L piping to three distribution points.
- Distribution Site 1: A vial washing station that will accept water at 80°C.
- Distribution Site 2: A wash sink requiring WFI at ≤ 40°C after passage through a heat exchanger.
- Distribution Site 3: A Compounding station that will require variable temperature delivery of water from a heat exchanger. Temperature range will be 23°C to 80°C.

Example 2 of URS: WFI Storage Tank

- WFI from the WFI-PS generation equipment is fed to the Storage Tank on a demand based on level.
- Storage Tank is maintained at 80 ± 2ºC by plant steam through a tank heating jacket. The tank temperature is used to adjust the set point of the temperature controller.
- WFI returning from the Hot WFI Circulation Loop is sprayed into Storage Tank through a Spray Ball to ensure that the tank's internal surfaces are completely and continuously wetted by hot WFI and are thus maintained in a sanitary and clean condition.
- The tank is maintained at atmospheric pressure by a steam-traced hydrophobic vent filter.
- All WFI contact surfaces are 316L stainless steel with a 20 µ inch Ra or better surface finish.

Biofilm formation



Biofilm formation

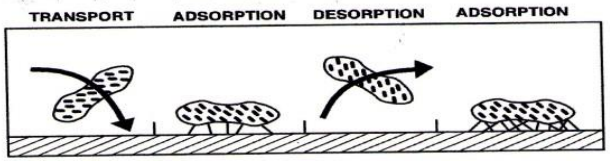


Fig. 2
Transport of bacteria cells to the conditioned surface, adsorption, desorption, and irreversible adsorption. (Characklis 1990)

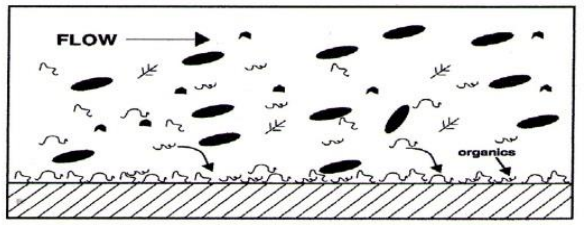


Fig. 1
Adsorption of organic molecules on a clean surface forms a conditioning film. (Characklis 1990)

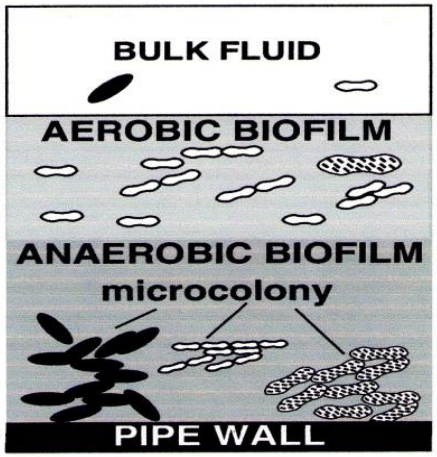


Fig. 5
Biofilm periodically releases a 'pioneer' cells

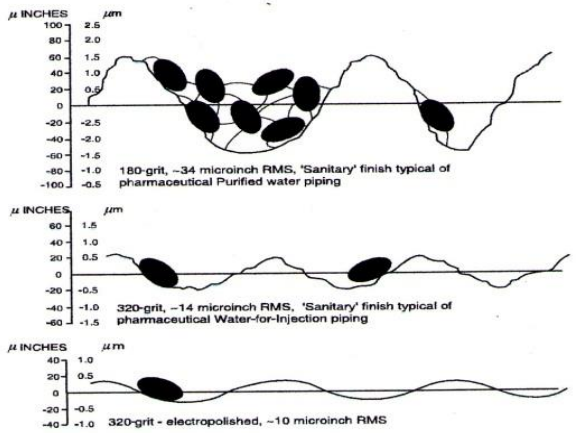


Figure 7.
Roughness profile of various stainless steel finishes

BIOFILM

Bacteria develop cooperative colonies within the biofilm. An anaerobic biofilm may develop underneath the aerobic layer. The biofilm thickness will reach an ***equilibrium*** *as flowing water* ***detaches cells*** *extending out into turbulent flow.* *(Borenstein 1994)*

How fast does biofilm develop?

Development of a mature biofilm may take several **several weeks or months** depending on the system. *Pseudomonas aeruginosa is a* common 'pioneer' bacteria in biofilms. Mittelman (1985).

Pseudomonas cells adhere to stainless steel, even to electropolished surfaces, within 30 seconds of exposure. (Vanhaecke 1990),

DESIGN QUALIFICATION

Design documents

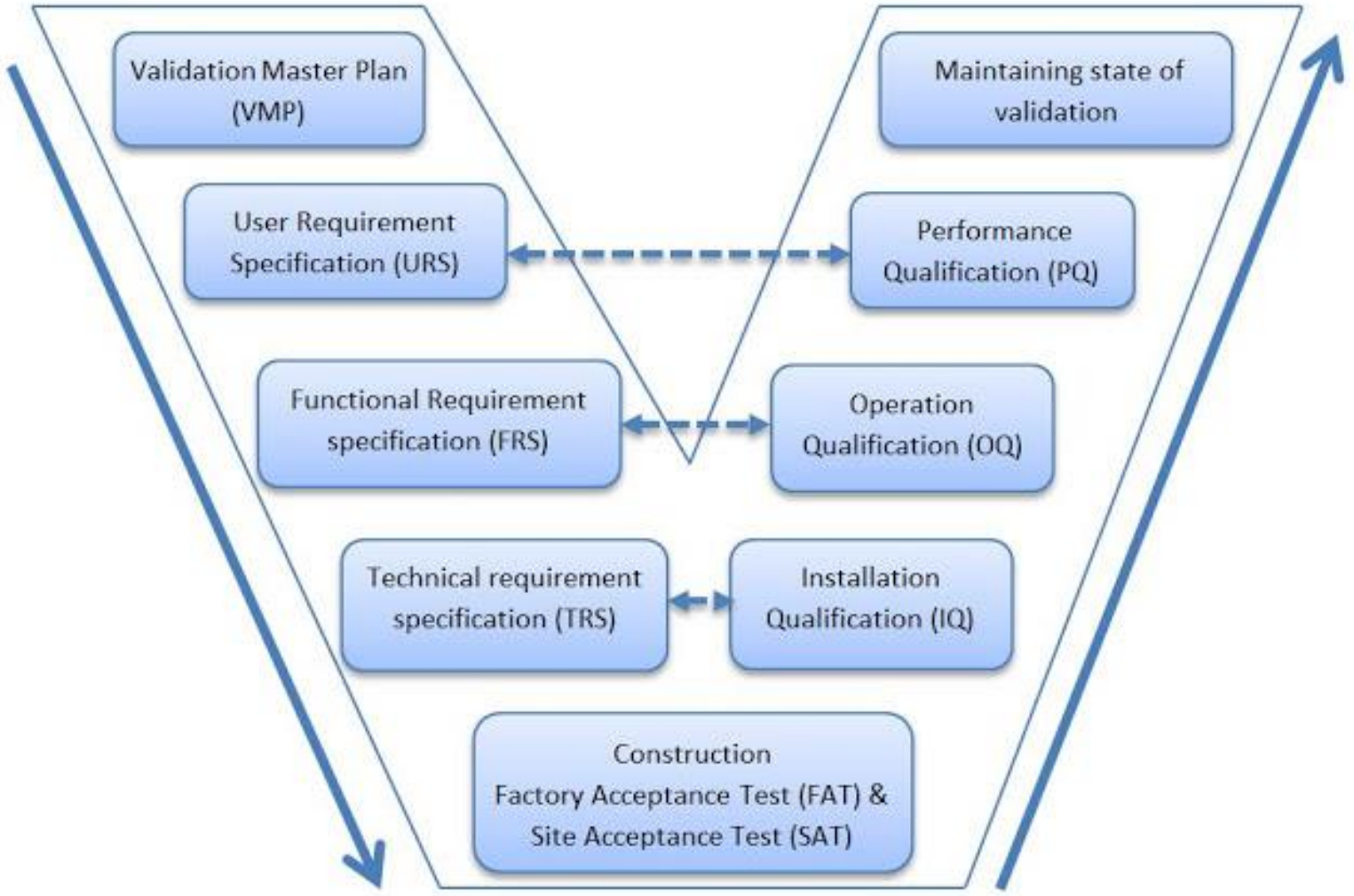
- piping and instrumentation diagram (P&ID)
- functional specification (FS); software design specification
- hardware design specification (HDS); electrical schematics
- layout drawing;
- component list; instrument list; valve list.

VALIDATION APPROACH

- The V-model: verification of the system according to the design

- The V-model provides a logical sequence that helps to organize the complex activities of defining a project scope, executing it, and qualifying it.

- The V model provides an excellent basis for design control and tracking design changes through the proceeding of the project.



DESIGN QUALIFICATION

- Verify design in relation to the URS (user's requirements specifications). Use traceability matrix in table form.

Design approval

- The design approval is a critical milestone.
- Review all design documents, drawings according to the URS.
- Use the validation protocol’s change control system

FAT & SAT

Factory / Site Acceptance tests = Use the opportunity !

- FAT: useful to check premanufactured units before they are sent to site.
- It is quick and efficient to make any changes to eliminate any deviations.
- Use the validation protocol's change control system as necessary
- During FAT and SAT, requirements will be tested according to good engineering practice (GEP).
- Clearly plan and state the strategy in the FAT/SAT protocol which tests are done in in each stage, and which are going to be repeated during IQ.
- Gain knowledge and train personnel who will be operating, maintaining and validating the system.

INSTALATION QUALIFICATION (IQ)

- Protocol driven. Include mechanical inspections, instrument calibrations, documentation. Training . External SOPs used by contractor.

- Review FAT/SAT reports at the start of the IQ to ensure that all deviations have been closed.

- Sequence of tests is critical (eg. slope of pipes measured before the distribution pipe is insulated).

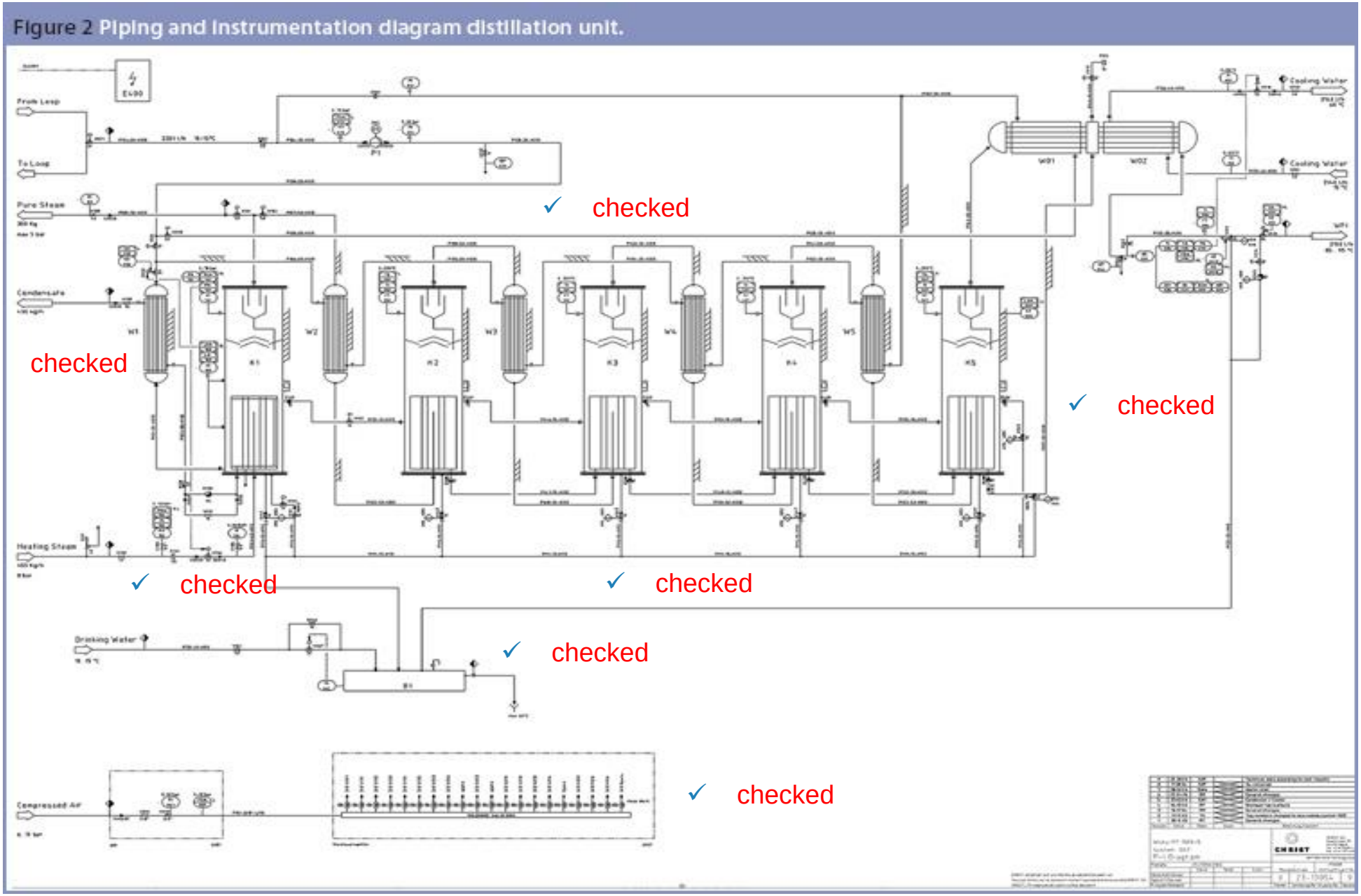
- Test Documentation: define which documents must be completed by when in the project. Test acceptance criteria. Test Method defined (measurement, visual verification, documentation, test). Test Evidence defined (document; manual record; instrument reading/print out).

- When IQ is finished and carefully reviewed, the result is presented in the IQ summary report. If no critical deviations were identified, the OQ can begin.

- Manage minor deviations as necessary.

✓ WPU P&ID "as-built" Drawings

Figure 2 Piping and instrumentation diagram distillation unit.



Material certification

TOP LINE
PROCESS EQUIPMENT COMPANY

P.O. Box 264
BRADFORD, PA 16701
Ph: 800-458-6095
Fax: 814-362-4453

MILL TEST SUMMARY

Order #: 00256350
Reference:
Order Date: 7/16/2007

Customer:

Part #: 40720-3 — TL2S 2" 90° ELL, BPE — Qty: 1 — 316L
Heat #: 816146 — 316/316L, 20RA ID / MILL OD

CHEMICAL COMPOSITION (WT%)									
Carbon	Mang	Phospur	Sulfur	Silicon	Chrom	Nickel	Nitrogen	Moly	Copper
0.016	1.830	0.028	0.007	0.410	16.400	10.500	0.030	2.120	0.320

MECHANICAL PROPERTIES				
Hardness	Yield Strength	Tensile Strength	Elongation(%)	Reduction (%)
87 RB	46260 PSI	84910 PSI	52	

RAW MATERIAL SPECIFICATIONS

ASME SA 249
ASTM A 269
ASTM A 270
EN 10 204 3.1 B

Part #: 401161510-3 — TL31 1 1/2 x 1 CONC RED, BPE — Qty: 3 — 316L
Heat #: 5105286 — 316/316L, 20RA ID / MILL OD

CHEMICAL COMPOSITION (WT%)									
Carbon	Mang	Phospur	Sulfur	Silicon	Chrom	Nickel	Nitrogen	Moly	Copper
.023	1.120	.034	.005	.450	16.560	10.210	N/A	2.060	N/A

MECHANICAL PROPERTIES				
Hardness	Yield Strength	Tensile Strength	Elongation(%)	Reduction (%)
83 HRB	353 N/MM2	619 N/MM2	42	N/A

RAW MATERIAL SPECIFICATIONS

ASTM A270
EN 10204 3.1B

✓ MOC checked as SS 316L equivalent

Assure proper correspondance between certificates and parts

We certify that the information contained in this Mill Test Summary was obtained from, and is a faithful representation of, the data furnished to us. The document from which this information was taken is on file in our office.

We certify that we have no knowledge of mercury or radioactive material used in the melting or processing of steel used in fittings sold by our company.

Timothy Fox
Quality Control Manager
Date: 7/26/2007
Time: 12:42 PM

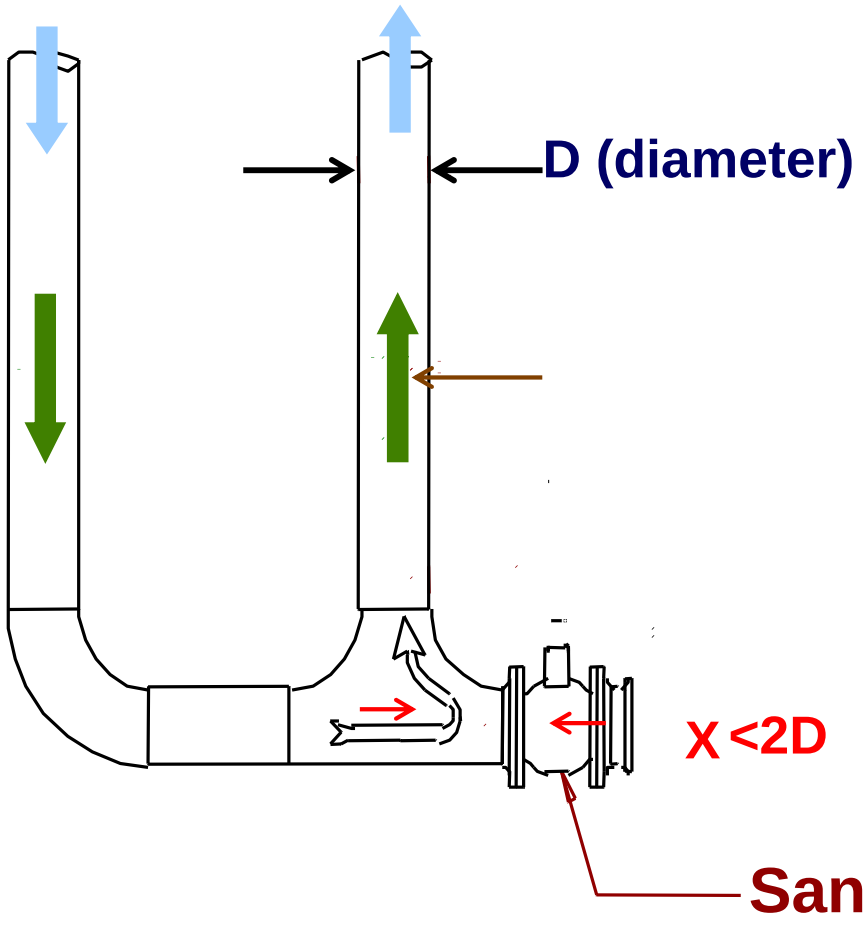
O-rings, seals, and gaskets

- **SD-3.6.4** All O-rings, seals, and gaskets in the product zones shall be compatible with the CIP cleaning media and SIP (e.g., steam-resistant elastomers/fluorelastomers).

- **SD-3.4.3** Materials shall be compatible with the stated bioprocessing conditions, cleaning solutions, and SIP conditions, etc., as specified by the owner/user.
- Surfaces exposed to bioprocessing fluids, cleaning, & SIP conditions must be:
- *(a)* homogeneous in nature
- *(b)* impervious
- *(c)* inert
- *(d)* nonabsorbent
- *(e)* nontoxic
- *(f)* insoluble by process or cleaning fluids
- *(g)* resistant to corrosion, scratching, scoring, and distortion

Verify absence of “dead legs” in IQ

“dead legs”



- **If D = 25mm, and the distance X is > 50 mm, then there is a dead leg.**

Welding verification

As per ASME (MJ-7.2.3). Tubing. Examinations including:

- Visual, liquid penetrant, radiographic, ultrasonic, etc.
- The external surfaces of all welds shall be visually examined.
- Personnel performing examinations of tubing systems shall meet requirements of ASME B31.3, Personnel Qualification and Certification.
- Owner/user, installing contractor, inspection contractor, and/or engineer shall agree to the minimum percentage of welds to be selected for **borescopic** or other internal visual examination.

Welding verification

As per ASME (MJ-7.2.3). Tubing. Examinations including:

- The contractor shall submit an inspection plan to ensure that welds meet the acceptance criteria of this Part. …a minimum of 20% of all welds shall be randomly selected in each separate system.

- There shall also be a plan for checking each operator ’s first shift of production. Examiners shall be qualified in accordance with ASME B31.3. Owner’s inspectors and inspectors’ delegates shall be qualified in accordance with GR-4.

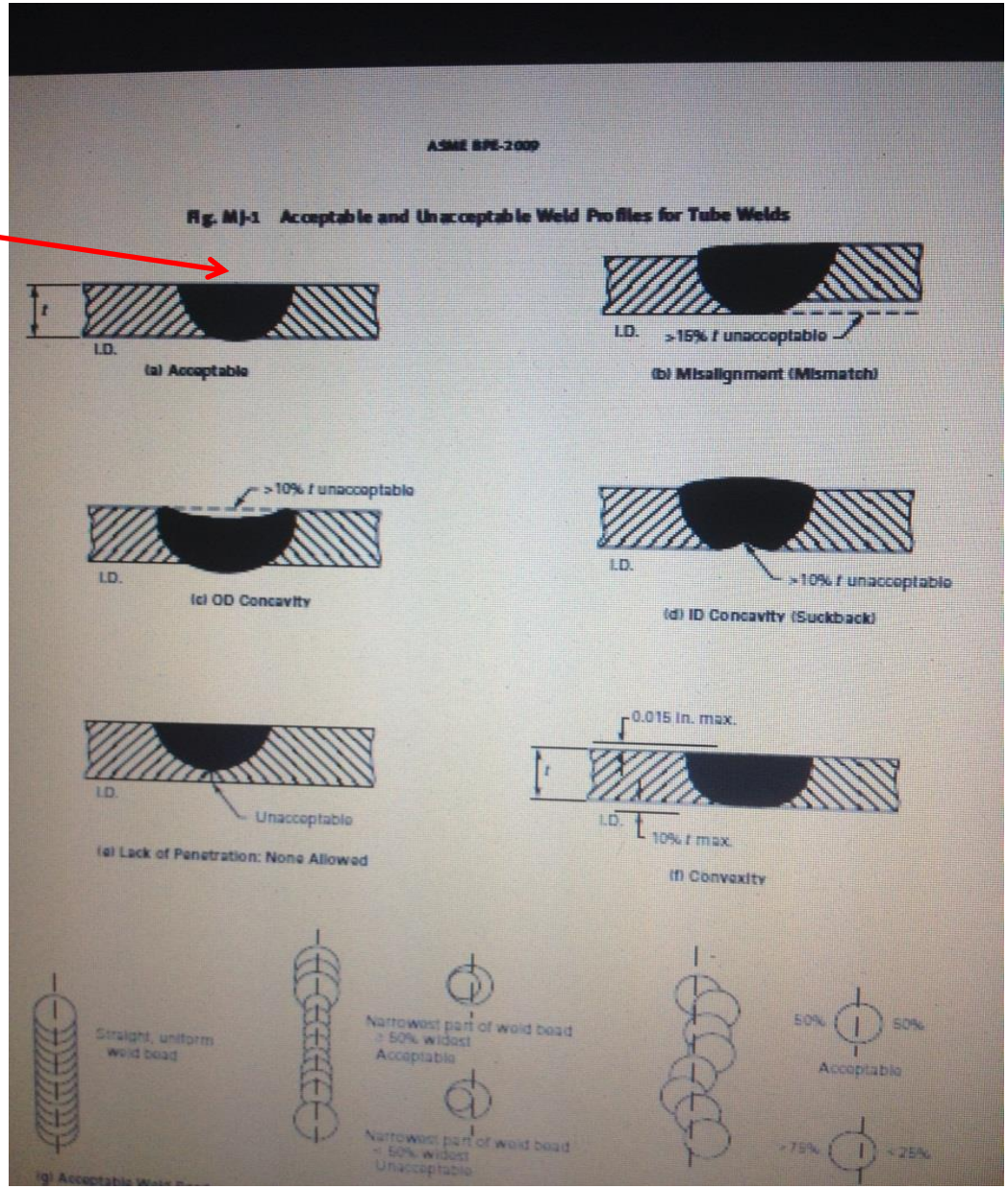
Welding

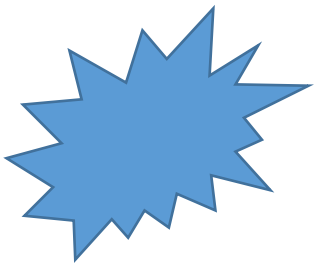
- Orbital Welding TIG: tungsten electrode.
- Welding aea protected from atmospheric gases by using an inert gas (e.g., Argon).
- Assure proper traceability and certification of Argon gas
- Welding does not add material

Boroscopy photos

Welding Quality is essential

Correct





Boroscopy video

- Is the welding acceptable based on the videos shown ?

Welding record

PLANILLA DE REGISTRO E INSPECCION DE SOLDADURAS

CLIENTE: | Pág. 10 de 10

PROYECTO N° (JOB N°): 890368 (nuevo: 160503b8) | UBICACION (LOCATION):

TITULO (TITLE): Siot. dmec. y diot. uri | PLANO DE REF. (REF. DRG.) N°: 11-999-2417-01-RO.DWG

SISTEMA N° (SYSTEM): MAT.: AISI 316L | NORMA: Asme BPE 2000a | OTROS:

Soldadura		Máquina	Procedim.	Probeta	Diámetro	Soldador		Ensayo no destructivo			Gas (Argón Int.)		Gas (Argón Ext.)		Supervisor	Cliente	Observaciones
Fecha	N°	N° serie	Soldadura	N°	Externo	Identificación	Firma	Visual	V.End.	Rx	Lote	Cilindro	Lote	Cilindro	Firma	Firma	
1-2-2012	035	30304	021	030	50,8	Condori Carlos		✓			56503	189425	56795	473945			
6-2-2012	146	30304	021	145	25,4	Condori Carlos		✓			56503	189425	56795	473945			
6-2-2012	147	30304	021	145	25,4	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	21	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	22	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	23	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	24	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	25	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	26	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	27	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	28	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	29	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	30	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	31	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			
14-2-2012	32	30304	021	20	19.01	Condori Carlos		✓			56503	189425	56795	473945			

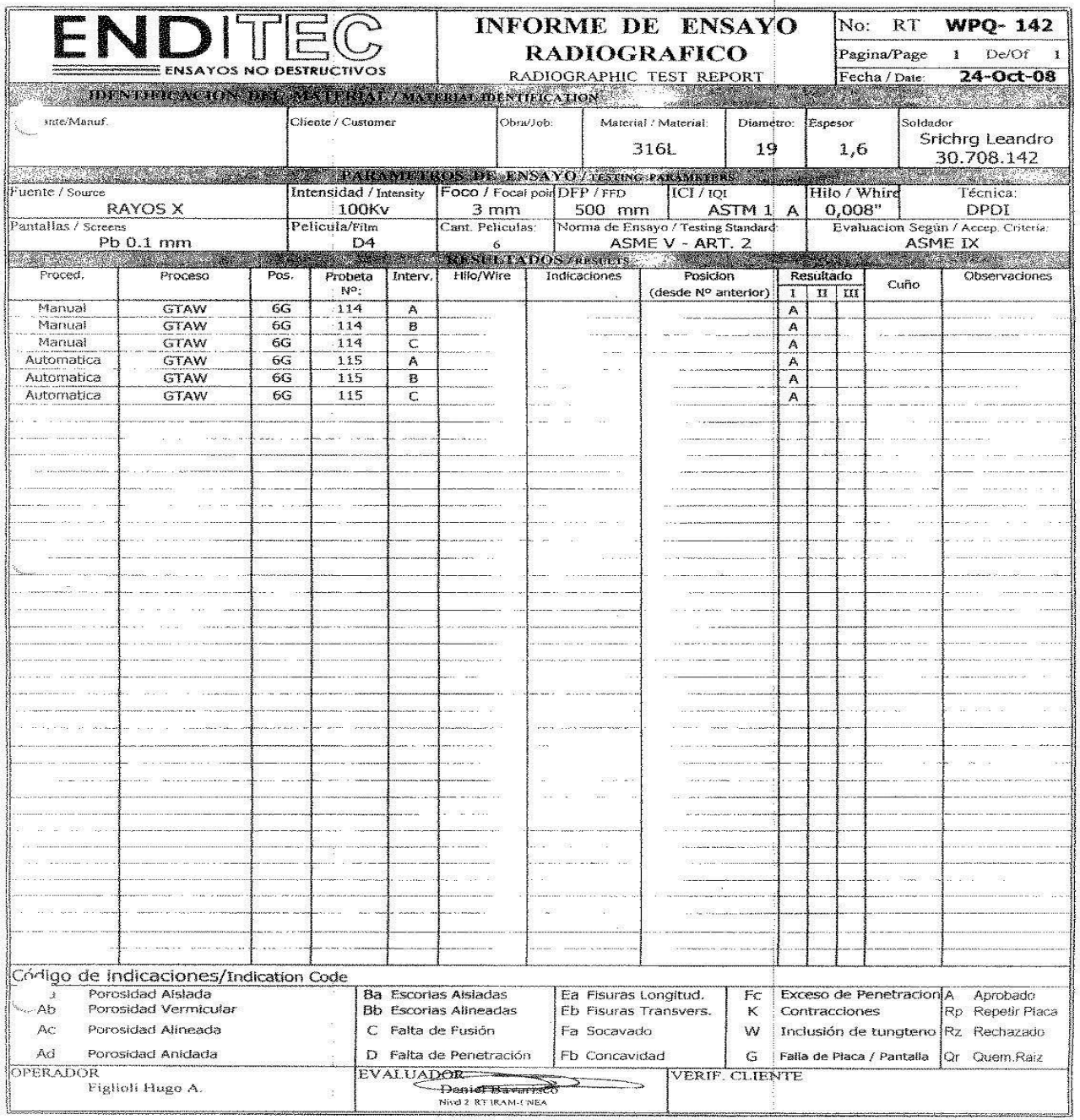
Declaración: Los datos registrados arriba han sido revisados.
(Declaration: Data recorded above has been reviewed).

Firma: (Sign) | Fecha: (Date)

Supervisado por: Checked by: Firma: (Sign) Fecha: 6-2-2012 (Date)

Por el Cliente: Customer: Firma: (Sign) Fecha: (Date)

X RAY Verification



ENDITEC — ENSAYOS NO DESTRUCTIVOS

INFORME DE ENSAYO RADIOGRAFICO
RADIOGRAPHIC TEST REPORT

No: RT **WPQ- 142**
Pagina/Page 1 De/Of 1
Fecha / Date: **24-Oct-08**

IDENTIFICACION DEL MATERIAL / MATERIAL IDENTIFICATION

Inte/Manuf.	Cliente / Customer	Obra/Job:	Material / Material:	Diametro:	Espesor	Soldador
			316L	19	1,6	Srichrg Leandro 30.708.142

PARAMETROS DE ENSAYO / TESTING PARAMETERS

Fuente / Source	Intensidad / Intensity	Foco / Focal poir	DFP / FFD	ICI / IQI	Hilo / Whire	Técnica:
RAYOS X	100Kv	3 mm	500 mm	ASTM 1 A	0,008"	DPDI

Pantallas / Screens	Pelicula/Film	Cant. Peliculas:	Norma de Ensayo / Testing Standard:	Evaluacion Según / Accep. Criteria:
Pb 0.1 mm	D4	6	ASME V - ART. 2	ASME IX

RESULTADOS / RESULTS

Proced.	Proceso	Pos.	Probeta Nº:	Interv.	Hilo/Wire	Indicaciones	Posicion (desde Nº anterior)	Resultado I	Resultado II	Resultado III	Cuño	Observaciones
Manual	GTAW	6G	114	A				A				
Manual	GTAW	6G	114	B				A				
Manual	GTAW	6G	114	C				A				
Automatica	GTAW	6G	115	A				A				
Automatica	GTAW	6G	115	B				A				
Automatica	GTAW	6G	115	C				A				

Código de indicaciones/Indication Code

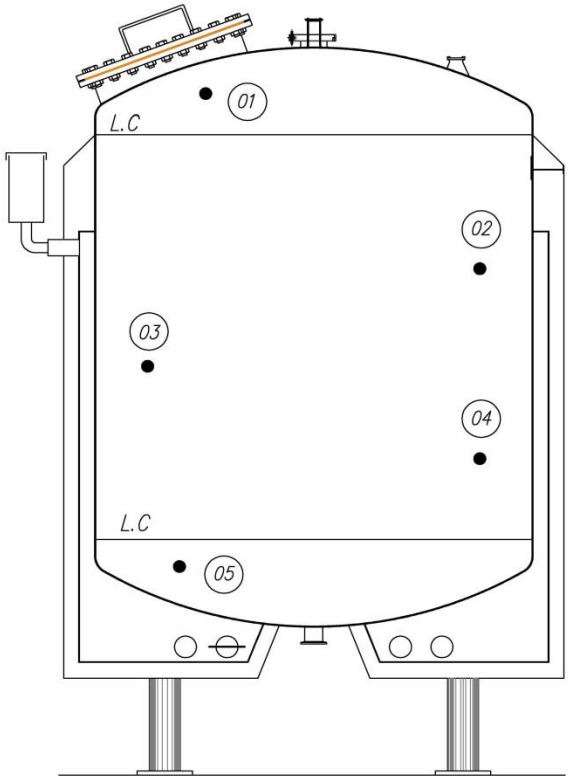
Porosidad Aislada	Ba Escorias Aisladas	Ea Fisuras Longitud.	Fc	Exceso de Penetracion	A	Aprobado
Ab Porosidad Vermicular	Bb Escorias Alineadas	Eb Fisuras Transvers.	K	Contracciones	Rp	Repetir Placa
Ac Porosidad Alineada	C Falta de Fusión	Fa Socavado	W	Inclusión de tungteno	Rz	Rechazado
Ad Porosidad Anidada	D Falta de Penetración	Fb Concavidad	G	Falla de Placa / Pantalla	Qr	Quem.Raiz

OPERADOR: Figlioli Hugo A.

EVALUADOR: Daniel Bavarco
Nivel 2 RT IRAM-CNEA

VERIF. CLIENTE

Internal surface polishing grade



ELEVACION

PUNTO	RUGOSIDAD
1	0,30 µm
2	0,25 µm
3	0,25 µm
4	0,35 µm
5	0,20 µm
6	0,30 µm

REVISION	DESCRIPCION	DIBUJO	CONTROLO	FECHA
0	CONFORME A OBRA	MBG	DD	14/06/12

APROBADO POR:

CLIENTE:

DIBUJÓ	FECHA	CONTROLÓ	FECHA	ESCALA (S)
MBG	14/06/12	DD	14/06/12	S/E

OBRA: TANQUE ALMACENAMIENTO WFI

PROYECTO N°

DESCRIPCION: TK-001 CAP.1500 LITROS PLANO DE RUGOSIDAD

PLANO N°: 11-9992498-EQ-02

REV. N°: 0

FORMATO A3 ESCALA PLOTEO: 1:1

ARCHIVO DWG: 11-9992498-EQ-02-RO.DWG

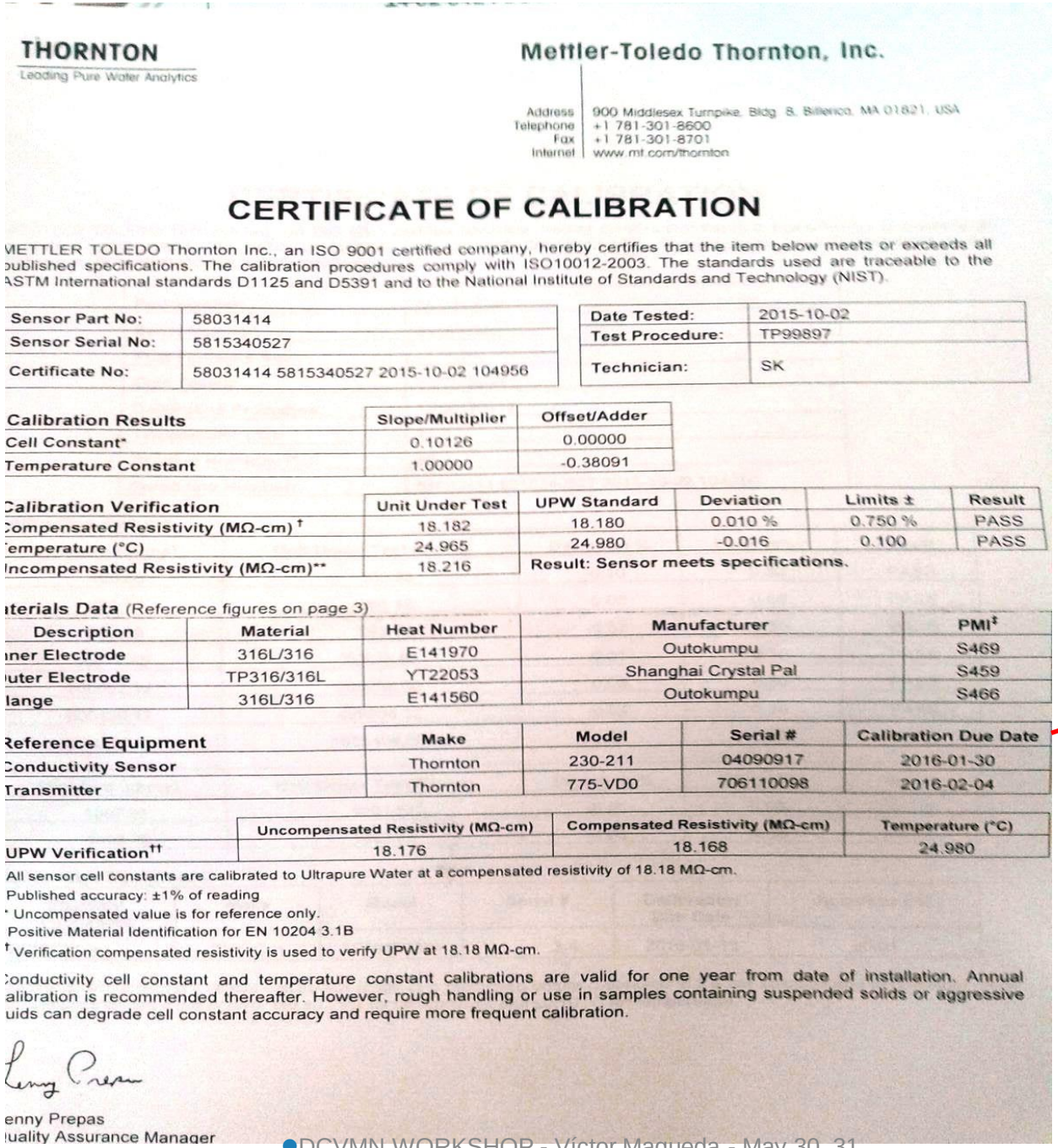
Drainability (ASME; SD-3.12)

- For the purpose of sterility and cleaning, gravity is an effective way to facilitate drainage.
- Pipe lines should be pitched to designated points at a specific slope.
- Appendix C for suggested method of slope measurement.
- The owner/user may define the system slope in accordance with one of the designations listed in Table SD-3 (> 0,5%).

Personal Note: Typically, > 0,5-1% for long sections, and > 1% for short ones.

- Product-contact lines should be sloped to minimize pooling of product in the system.
- Lines that are steam sterilized in-place should be sloped to facilitate gravity drainage of condensate.
- Lines that are cleaned in-place should be sloped to facilitate gravity drainage of cleaning fluids.

Calibration



THORNTON
Leading Pure Water Analytics

Mettler-Toledo Thornton, Inc.

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Internet: www.mt.com/thornton

CERTIFICATE OF CALIBRATION

METTLER TOLEDO Thornton Inc., an ISO 9001 certified company, hereby certifies that the item below meets or exceeds all published specifications. The calibration procedures comply with ISO10012-2003. The standards used are traceable to the ASTM International standards D1125 and D5391 and to the National Institute of Standards and Technology (NIST).

Sensor Part No:	58031414
Sensor Serial No:	5815340527
Certificate No:	58031414 5815340527 2015-10-02 104956

Date Tested:	2015-10-02
Test Procedure:	TP99897
Technician:	SK

Calibration Results	Slope/Multiplier	Offset/Adder
Cell Constant*	0.10126	0.00000
Temperature Constant	1.00000	-0.38091

Calibration Verification	Unit Under Test	UPW Standard	Deviation	Limits ±	Result
Compensated Resistivity (MΩ-cm)†	18.182	18.180	0.010 %	0.750 %	PASS
Temperature (°C)	24.965	24.980	-0.016	0.100	PASS
Uncompensated Resistivity (MΩ-cm)**	18.216	Result: Sensor meets specifications.			

Materials Data (Reference figures on page 3)

Description	Material	Heat Number	Manufacturer	PMI‡
Inner Electrode	316L/316	E141970	Outokumpu	S469
Outer Electrode	TP316/316L	YT22053	Shanghai Crystal Pal	S459
Flange	316L/316	E141560	Outokumpu	S466

Reference Equipment	Make	Model	Serial #	Calibration Due Date
Conductivity Sensor	Thornton	230-211	04090917	2016-01-30
Transmitter	Thornton	775-VD0	706110098	2016-02-04

	Uncompensated Resistivity (MΩ-cm)	Compensated Resistivity (MΩ-cm)	Temperature (°C)
UPW Verification††	18.176	18.168	24.980

All sensor cell constants are calibrated to Ultrapure Water at a compensated resistivity of 18.18 MΩ-cm.
Published accuracy: ±1% of reading
* Uncompensated value is for reference only.
‡ Positive Material Identification for EN 10204 3.1B
† Verification compensated resistivity is used to verify UPW at 18.18 MΩ-cm.

Conductivity cell constant and temperature constant calibrations are valid for one year from date of installation. Annual calibration is recommended thereafter. However, rough handling or use in samples containing suspended solids or aggressive fluids can degrade cell constant accuracy and require more frequent calibration.

Jenny Prepas
Quality Assurance Manager

✓ Calibration due date of standard used checked.

Exercise: verify URS

OPERATION QUALIFICATION

- Protocol driven. Verify operation according to the Functional Specifications (FS): conductivity, temperature, flow, water quality. Training requirements

- Test operational parameters. Evaluate alert and action levels, which form the basis for the alarms generated by the system.

- Test Documentation: Test acceptance criteria. Test Method defined (measurement, visual verification, documentation, test). Test Evidence defined (document; manual record; instrument reading/print out). Calibration required. External SOPs used by contractor.

- When all tests are performed and reviewed, the result of the OQ is presented in the OQ summary report. If no critical deviations were identified, the PQ can start. Manage minor deviations as necessary.

Example of OQ test: Spray Ball

- **SD-5.1 Spray Ball Test**
- The purpose of a spray ball test is to document proper fluid coverage of the internal surface and parts of a tank or piece of equipment.

- The test shall be performed by spraying a dye (e.g., riboflavin) on the entire interior of the equipment product/process contact walls, nozzles, and miscellaneous surfaces.

Documentation Package for the water treatment & distribution system

Assure that the structure of the documentation is:

- logical
- clear
- simple and user-friendly (eg. Index; from general-to-specific technical data binders--traceable)

- Traceable matrix showing in which protocols and tests the requirements will be met.

- Decisions must be justified and followed to obtain consistency in the documentation.

- The system owner or subject matter expert (SME) should understand the train of thought.

Documentation Package for the water treatment & distribution system

Assure that the structure of the documentation is:

•Meets Good documentation practice (GDP). Nothing must be left incomplete and empty.

- Execution must be followed by an efficient review to detect whether anything is incomplete, or has not been described or referred to in a logical way.

- Changes to the test method and to the installation described and reviewed in detail.

- Deviations clearly described and assessed in terms of risk. Categorize them. Mentioned in summary report.

Good Documentation Practices (GDP)

Table 1 A traceability matrix showing in which protocols and tests the requirements will be met.

URS	Request number	QC Description	Protocol	Test
URS.2301-01	3.2.1	All instrumental-mounting sites (measurements sites) must be marked with the TAG number, indicated in the P and I diagram.	FAT-50303-01 SAT-50303-04	FAT03 SAT02

PERFORMANCE QUALIFICATION

3-phase approach:

Phase I

(2-4 weeks)

Water is not used for commercial manufacturing

- Undertake chemical and microbiological testing in accordance with a defined plan.
- Sample or continuously monitor the incoming feed-water daily to verify its quality.
- Sample or continuously monitor after each step in the purification process.
- Sample or continuously monitor at each point of use and at other defined sample points.
- Develop appropriate operating ranges.
- Develop and finalize operating, cleaning, sanitizing and maintenance procedures.
- Demonstrate production and delivery of product water of the required quality and quantity.
- Use and refine the standard operating procedures (SOPs) for operation, maintenance, sanitization and troubleshooting.
- Verify provisional alert levels.
- Develop and refine test-failure procedure.

PERFORMANCE QUALIFICATION

3-phase approach

Phase II

(2-4 weeks)

Same sampling scheme as phase I

- demonstrate consistent operation within established ranges;
- demonstrate consistent production and delivery of water of the required quantity and quality when the system is operated in accordance with the SOPs.

- WHO TRS 970: “Use of the water for manufacturing purposes during this phase may be acceptable, provided that both commissioning and phase 1 data demonstrate appropriate water quality and the practice is approved by QA”.

Not a standard practice !

PERFORMANCE QUALIFICATION

3-phase approach

Phase III

(completes a year study)

- to demonstrate reliable performance over an extended period;
- to ensure that seasonal variations are evaluated.

The sample locations, sampling frequencies and tests should be reduced to the normal routine pattern based on established procedures proven during phases 1 and 2.

Water can be used for production purposes

Water sampling

- For Total Aerobic Count, FDA: “With regard to sample size, **100 - 300 mL** is preferred when sampling Water for Injection systems. Sample volumes less than 100 mL are unacceptable”.

- Detect P*. aeruginosa* and *E. coli*)

- Incubate at 30-35C for 48-72 hours (USP) or 5 days (EP)

Microbiological specifications of WFI & PW

- BET (Bacterial Endotoxin Limit): 0.25 EU/ml

- Microbial limit:

WFI: **10 CFUs/100 ml**;

PW: **100 CFU/ml**;

- R2A agar must be used

- Potable water / well: 500 CFU/ml, y comply with standards WHO Guidelines for drinking-water quality, o locales

Physicochemical Specifications of WFI & PW

- CONDUCTIVITY: Meets USP Stage I, II, o III (e.g., 1.3 Us/cm @ 25 C); reading is not compensated by temperature.
- Total Organic Carbon (TOC): < 500 ppb
- Tests Adicionales según EP

Pure Steam Monitoring

- Some microbes are so heat resistant that they can grow in steam systems
- Anywhere in the steam system where condensation is present, creates a particular contamination risk
- Steam is hooked to a portable condenser, turned to water, and the water tested like other liquid monitoring

Pure Steam

- Same specs as WFI
- Micro testing not required by EP
- Additional specifications:
  - Steam Dryness >90%
  - Superheated steam <25º C
  - Non-Condensable gases <3.5%

Pure Steam

- “…small quantities of **noncondensable gases** or **superheated or dry state**, may also be important in sterilization. If condensation is not allowed to happen because the steam is extremely hot and in a persistent superheated, dry state, then its usefulness **could be seriously compromised**.

- Noncondensable gases in steam tend to stratify or collect in certain areas of a steam sterilization chamber or its load. These surfaces would thereby be at least partially insulated from the steam condensation phenomenon, **preventing them from experiencing the full energy of the sterilizing conditions**.

USP 35 "Pure Steam“ <1231> "Water for Pharmaceutical Purposes".

Non-condensable gases (inert gases)

Pure Steam Monograph (USP 29, valid since 01.04.2006)

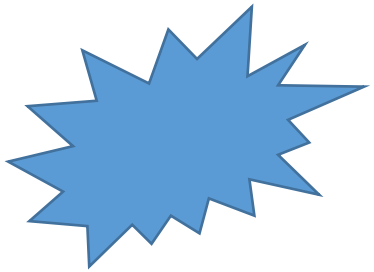
- Mainly NH3 (Ammonia), CO2, N2, O2 and halogenated Hydrocarbons

- Why we have to test non-condensable gases for steam quality?

- To demonstrate that the level of non-condensable gases contained in the steam will not prevent the attainment of sterilization conditions in any part of the sterilizer load.

- Measurement according to EN 285

"The sterilizer shall be designed to operate with dry saturated steam containing not more than 3,5 % V/V non-condensable gases …"



Audit Finding

Identify the deviations, assess impact on the product, propose CAPA:

During review of PW trend analysis, several counts with 20-40 CFU/ml were observed. Historical values were below 1 CFU/ml. Alert levels were set at 50 CFU. No action was taken. These samples were drawn after maintenance activities (valve “O” ring change and filter change). There was no documented training of involved personal, and the activity was done based on an uncontrolled contractor's manual, with no indication of precautions for avoiding contamination. There was no control of the spare parts in the Maintenance department. It was unclear if the O rings could withstand steam sterilization temperatures during the system’s sanitization procedures.

References

- PI 009-X Inspection of Utilities- Aide Memoire- PICS (*PI 009-3, September 2007*)
- TRS 937, Annex 4 Supplementary guidelines on good manufacturing practices: validation. 2006.
  - Appendix 2 Validation of water systems for pharmaceutical use
- TRS 970 Annex 2 WHO good manufacturing practices: water for pharmaceutical use. 2012

THANK YOU