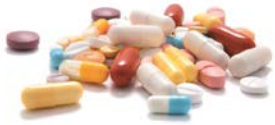


EXPERT
SANTÉ CANADA
MAPAQ

CLEAN UTILITIES
Purified Water – PW - WFI
from sanitary Conception to Validation

PBE-Expert Inc – CANADA

Accredited training organisation CPMT #0059104

Qualified MAPAQ Consultant

To the measure 2 of the "Levier" program

PBE, Training Company Agreement **CPMT** #0059104

Commission des partenaires du marché du travail
Québec

CERTIFICAT D'AGRÉMENT

Loi favorisant le développement et la reconnaissance des compétences de la main-d'oeuvre

Titulaire : PBE, PHARMA BIO EXPERT INC.

Numéro d'agrément : 0059104

NEQ : 1168916956

Catégorie d'agrément : Organisme formateur

Date de délivrance : 6 février 2018
Date d'échéance : 5 février 2020

CHAMPS PROFESSIONNELS

01 Administration et commerce
03 Alimentation, hôtellerie et tourisme
06 Chimie et biologie

Par : Isabelle Bergeur

Le 7 février 2018

La délivrance du certificat est valide en fonction des documents soumis à la Commission des partenaires du marché du travail.

Ministère du Travail, de l'Emploi et de la Solidarité sociale

EQ-6282 (06-2003)
ENT-0031 (12-2016)

Training goals / Clean Utilities
Purified Water PW

Part 1 – Which water type for which pharmaceutical use?
Part 2 – Which technology?

a. Pretreatment
b. Treatment
c. Polishing (Final treatment)
d. Storage tank
e. Distribution loop

Part 3 – Sanitary Design (ASME-BPE) of critical equipment
Part 4 – Equipment selection
Part 5 – Control & Instrumentation
Part 6 – Commissioning FAT, SAT, & IQ, OQ Validation
Part 7 – Quiz - evaluation

Training goals / PW – Part1

1. Introduction to pharmaceutical water uses.
2. What is the first step for a PW project?
3. What are the user requirement specifications (URS)?
4. Pharmaceutical water sources and types
5. Step 1 : Water pretreatment
6. Water for GMP Applications
7. Criteria for Purified Water in the United States Pharmacopea (USP) versus the European Pharmacopea (PhEur)
8. Group quiz

Training goals / PW – Part1

1. Temperature impact on conductivity.
2. Pharmaceutical water sources and types.
3. Water types for:
   a. Pharmaceutical processes
   b. Laboratories
4. References EMA, ISPE …. :
5. Which water for which process according to the FDA and EMA?
6. Active Pharmaceutical Ingredients (API), sterile and non sterile medication, injectable, Water for Injection (WFI), final rinse ?
7. Group exercise
5. Decision diagram

Purified Water (PW) unit in 9 points

1. What is a PW unit?
2. Benefits of a PW unit?
3. Why use PW?
4. How does a PW unit work?
5. PW unit details
6. PW unit types
7. EDI vs PW !
8. Monitoring, adjusted or not in temperature
9. Design considerations

Which design for which usage?

1. Which water analysis are to be provided?
2. Which quality needs to be obtained depending on sampling points?
3. Standards, alert level, level of action
4. What are the quantitative and evolutive needs (instant maximum, daily, weekly, seasonal,…)
5. Which are the applicable regulations?
6. What utilities are available (type, specifications) ?
7. What are the implementation constraints? Equipment purchase sources?

Which design for which usage?

8. **Defining sampling points:**
   a. Manual ?
   b. Automatic ?
   c. Localization ?
   d. Sampling flows ?
   e. Priorities ?
   f. Pressure ?
   g. Temperature ?...

Which design for which usage?

9. *What path to use for distribution?*
10. *What support?*
11. *What type of insulation ?*
12. *Which slopes and towards which equipment?*
13. *What drainability?*
14. *What velocity or turbulence?*
15. *What type of disinfection/sanitation?*

Which design for which usage?

16. *What automation for implementation?*
17. *What are the Critical Process Parameters (CPP)?*
18. *Which certificates to produce:*
    a. *Factory calibration ?*
    b. *On-site calibration ?*
    c. *Measuring chain?*
    d. *Filter integrity tests ?*
    e. *Passivation ?*
    f. *Orbital welding ?*

Which design for which usage?

19. What environmental constraints ?
20. What security constraints?
21. What maintenance constraints?
    a. How ?
    b. Frequencies ?
    c. Preferred brands ?...

Which design for which usage?

21. **Deadline?**
22. **What schedule ?**
    a. for service offer handing over ?
    b. for the exécution ?
22. **What documents are expected ?**
    a. Plans and diagrams,
    b. URS, technical files,
    c. Maintenance records,...?
    d. Who provides the As Built ?
23. **What qualifications are expected ?**
24. **What are the expected performance: CPP, Alerts and Alarms thresholds/ranges ?**
25. **What is the training for factory, operation, qualification and maintenance staff ?**

Regulatory framework: Cleaning (BPF/cGMP)

Regulatory framework: (BPF/cGMP)

World Health Organization (WHO)

- http://www.who.int/medicines/areas/quality_safety/quality_assurance/production/en/index.html

EU - EMEA

- http://ec.europa.eu/enterprise/pharmaceuticals/eudralex/vol4_en.htm

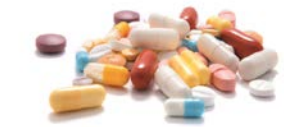
United States – FDA 21 CFRs

- http://www.fda.gov

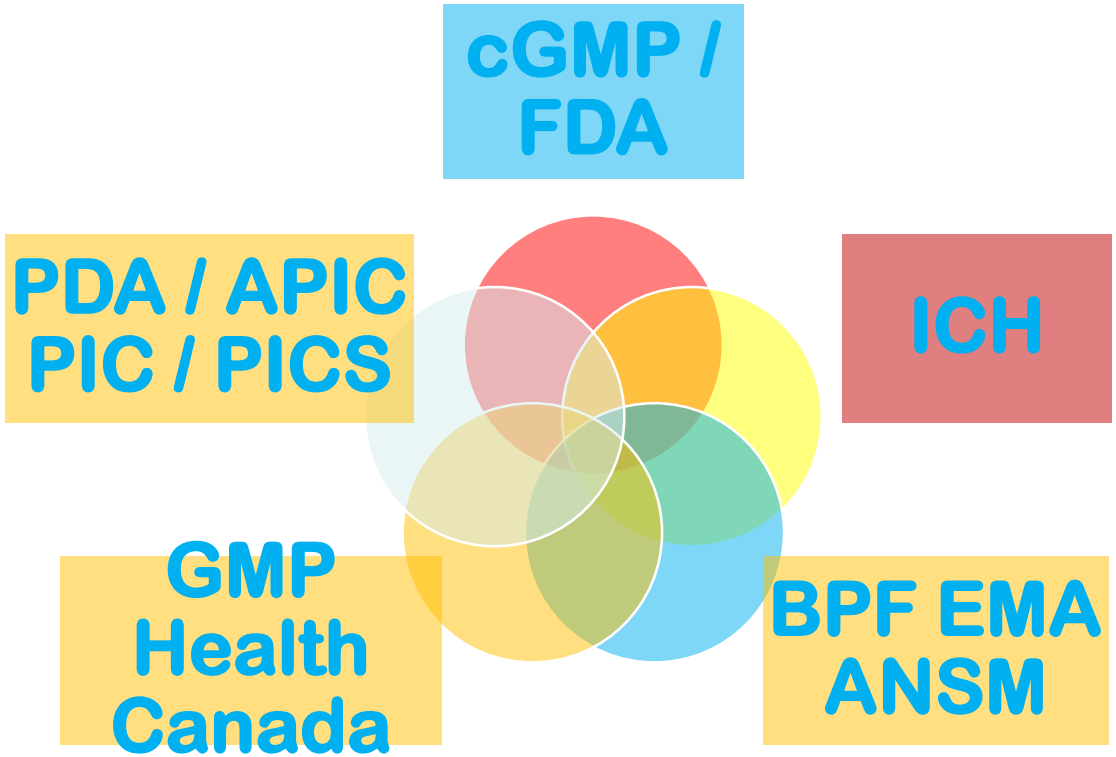
Canada – Health Canada

- http://www.hc-sc.gc.ca/dhp-mps/compli-conform/gmp-bpf/index-eng.php
- ICH = International Conference on Harmonization

http://www.ich.org/products/guidelines/quality/quality-single/article/good-manufacturing-practice-guide-for-active-pharmaceutical-ingredients.html



Laws & regulations vs countries ?



Normative requirements

- ✓ European Pharmacopoeia (Ph.Eur.)
- ✓ French Pharmacopoeia (Ph.F.)
- ✓ Pharmacopoeia Internationalis (Ph.I.)
- ✓ The British Pharmacopoeia (B.P.)
- ✓ The Canadian Formulary (C.F.)
- ✓ The National Formulary (N.F.)
- ✓ The Pharmaceutical Codex: Principles and Practices of Pharmaceuticals
- ✓ The United States Pharmacopoeia (U.S.P.)

Codes & Standards requirements

AABC	:	Associated Air Balance Council
ANSI	:	American National Standards Institute
ASHRAE	:	American Society of Heating Refrigerating and Air conditioning Engineers
ASME	:	American Society of Mechanical Engineer
BPE	:	ASME Bioprocessing Equipment (American Society of Mechanical Engineers)
ASTM2500	:	American Standard of Testing Materials
CRN	:	Canadian Registration Number (Pressurized equipment)
CSA	:	Association Canadienne de Normalisation

Requirements of Codes & Standards

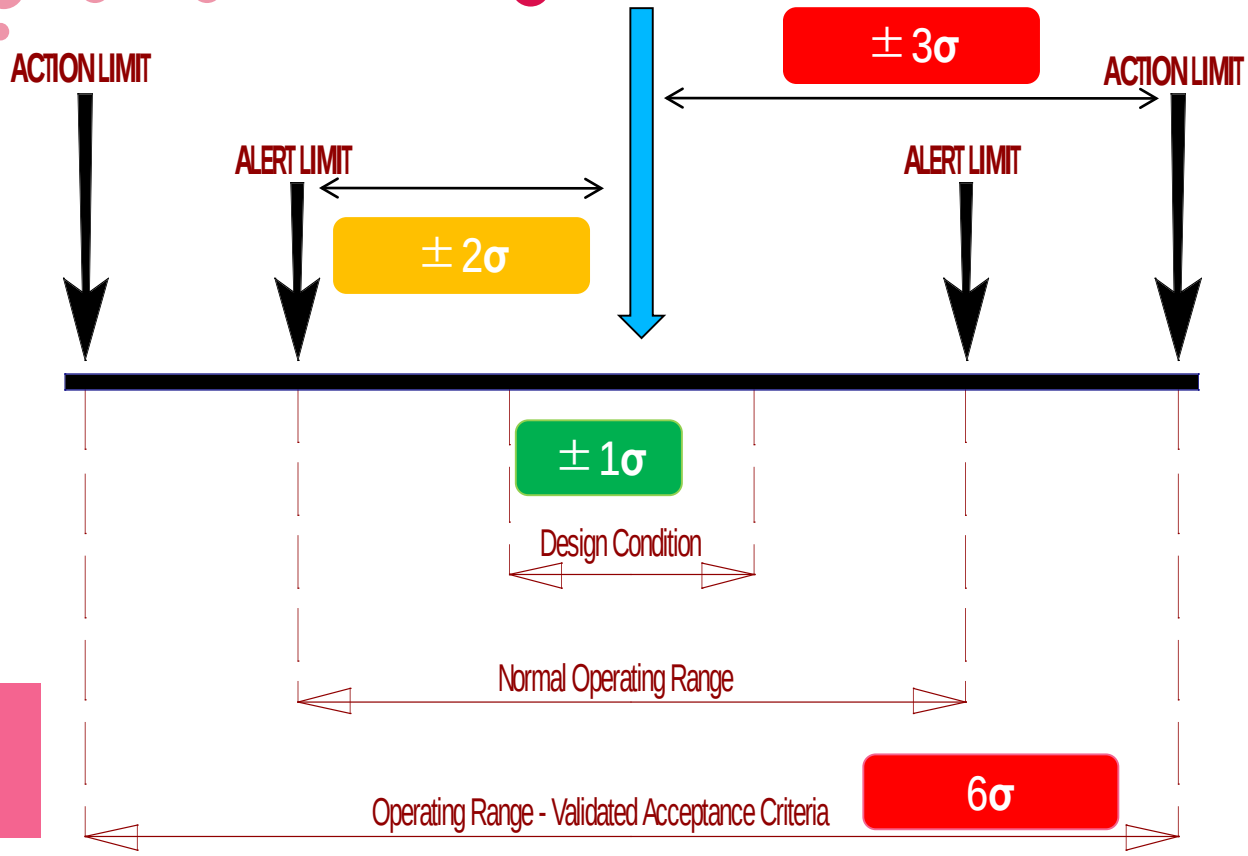
ISA	:	Instrument Society of America
NABC	:	National Air Balance Council
NEBB	:	National Environmental Balancing Bureau
NFPA	:	National Fire Protection Association
NEMA	:	National Electrical Manufacturers Association
OSHA	:	Occupational Health and Safety Administration
NIST	:	National Institute Of Standards and Technology
SMACNA	:	SMACNA Sheet Metal and Air Conditioning Contractors' National Association
ATEX	:	Explosive Atmosphere

URS

User requirements Analysis

URS : DESIGN APPROACH

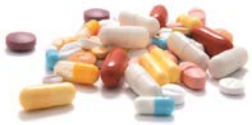
- Design conditions
- Normal operating ranges set to achievable limits
- Alert Points (2*Sigma)
- Action Points (3*Sigma)
- OOS results recorded



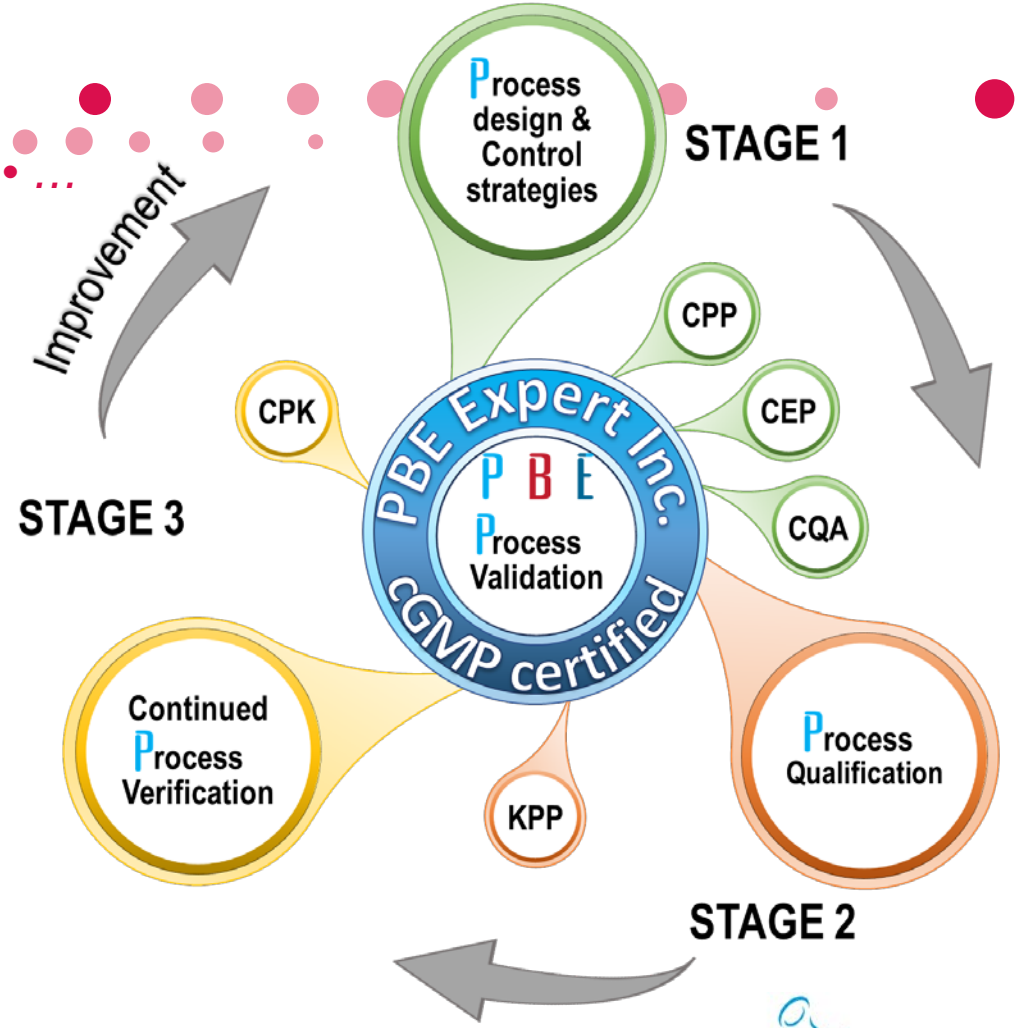
Action Limit = average +/- 3 sigma
Alert Limit= average +/- 2 sigma
Sigma = standard deviation/1,128

URS : 1- Performance Criteria:

1. Standards and Regulatory Framework
2. Performance Criteria
3. Operation Specifications
4. Installation Specifications
5. Simple process diagrams
6. Rational & references
7. Tests to plan
8. Execution in:
   a. IQ/OQ/PQ Validation
   b. and/or in Commissioning: FAT, SAT.

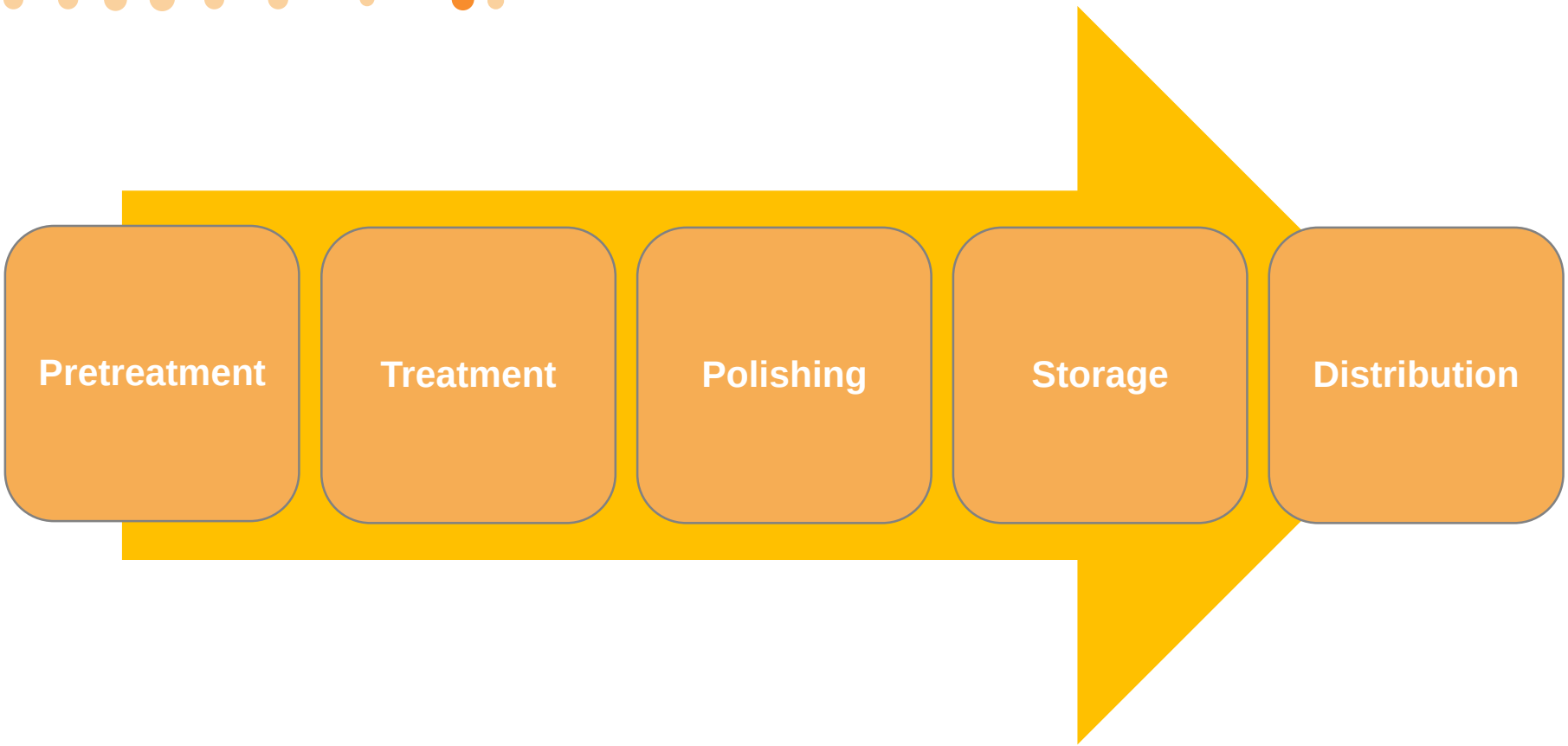


URS : LIFE CYCLE APPROACH – PROCESS VALIDATION



Standard process for removing Contaminants in water

Standard process for removing Contaminants in water



Standard process for removing Contaminants in water

1- Pretreatment steps

1. Primary filtration
2. Softening
3. Sanitation
4. Controls

Standard process for removing Contaminants in water

1- Pretreatment steps

1. Control and reduce the content of chemical & bacteriological products in accordance with acceptable concentrations (USP, PhEur, etc.).
2. Control and reduce microbial growth.
3. Systems must be properly validated.
4. Parenteral water should be free of pyrogens or endotoxins (USP, PhEu threshold limit).
5. Appropriate specifications and disinfection and periodic tests are required.

PW & WFI vs CPP according to USP & PhEu

CPP	WFI	USP Reference	PW	USP Reference	PhEu	PhEu Référence
Feed	Treated water	USP <1231>	Potable water	USP <1231>	Potable water	EP 07/2002:0008
Conductivity	≤ 1.1 µS/cm at 20° C ou ≤ 1.3 µS/cm at 25° C	USP <645>	≤ 1.3 µS/cm at 25° C	USP <645>	≤ 4.3 µS/cm at 20° C	EP 07/2002:0008
TOC	≤ 500 ppb	USP <643>	≤ 500 ppb	USP <643>	≤ 500 ppb	EP 07/2002:0008
Bacteria	≤ 0.10 UFC/mL	USP <1231>	≤ 100 UFC/mL	USP <1231>	≤ 100 UFC/mL	EP 07/2002:0008
Endotoxin	< 0.25 EU/mL	USP <1231>	N/Ap.	N/Ap.	< 0.25 EU/mL (note 1)	EP 07/2002:0008
Nitrates	N/Ap.	N/Ap.	N/Ap.	N/Ap.	≤ 0.2 ppm	EP 07/2002:0008
Heavy metals	N/Ap.	N/Ap.	N/Ap.	N/Ap.	≤ 0.1 ppm	EP 07/2002:0008
Aluminium	N/Ap.	N/Ap.	N/Ap.	N/Ap.	≤ 10 µg/L (note 1)	EP 07/2002:0008
Particles 0.22 µm	N/Ap.	N/Ap.	N/Ap.	N/Ap.	N/Ap.	N/Ap.
Pyrogens	N/Ap.	N/Ap.	N/Ap.	N/Ap.	N/Ap.	N/Ap.

Note 1: Applicable if water is used in the manufacture of dialysis solutions

3- What usage for which Process - Water types

3- What Usage for Which Pharmaceutical Process?

Table 6-1 General Guidance Only

System	Type: Process (P) or Process Support (PS)	GMP Important	Documentation/ Commissioning	Filter Requirements (Baseline)
Purified Water and WFI	P	Yes	Enhanced	N/A
Clean Steam	P	Yes	Enhanced	N/A
Nitrogen and other Process Gases	P	Yes	Enhanced	Endpoint 0.2µm for sterility 5µm for pre-filtration
Instrument Air	PS	No	GEP (= Good Engineering Practice)	N/A
Breathing Air	PS	No	GEP	N/A
Heating/Cooling	PS	No	GEP	N/A
Process Vacuum	P	Yes	Enhanced	See specific equipment item
Potable Water	PS	No	GEP	N/A
Mechanical Seal Fluids	Depends on use	Depends on use	GEP	N/A
Chilled Water	PS	No	GEP	N/A

ISPE vol.3, p79

3- Water types for Laboratories and Hospitals

1. Potable water (EPA, Drinking Water Regulations)
2. Softened water (CLSI - Type I, II, III)
3. Dionized water (CLSI - Type I, II, III)
4. Reverse osmosis water (CLSI - Type I, II, III)
5. Purified water
6. Water to feed the pure steam generators
7. Water to produce clean steam (HVAC, surgery rooms, ...)
8. Water for cooling autoclaves
9. Water for final rinse
10. WFI

3- Pharmaceutical water types

1. Undrinkable, industrial.
2. Drinkable.
3. Purified water (USP / PhEu).
4. Feed water for pure steam generators
5. Water to produce clean steam (HVAC, clean rooms, ...)
6. WFI.
7. Sterile WFI / USP.
8. Sterile water for inhalation / USP.
9. Bacteriostatic WFI / USP.
10. Purified sterile water for irrigation / USP.

3- Which water for which pharmaceutical process ?

1. Added as an ingredient to the pharmaceutical process.
2. Process support utility (Buffer / Media tank, Biofermentor, Formulation, etc.).
3. Initial / final rince: CIP. Washing machines, …
4. Produce Pure Steam, Clean Steam, WFI.
5. Pharmaceutical systems clean support utilities :
   a. Autoclaves.
   b. PAV liquid ring.
   c. Misting ….

3- Which pharmaceutical water for which process ?

1. Sterile drugs
2. Non sterile drugs
3. API production
4. Medical product manufacturing that is not present in the final formulation
5. Equipment and AC cleaning / rinsing.

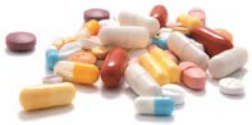
3- Which pharmaceutical water for which process ?

Water specifications	USP FDA	PhEu EMEA	Comments
Acceptable WFI produced by			
WFI quality monitored by TOC			
Highly Purified Water (HPW)			
Endotoxin & Bioburden Control			

3- Which pharmaceutical water for which process ?

1- Sterile Medicinal Products

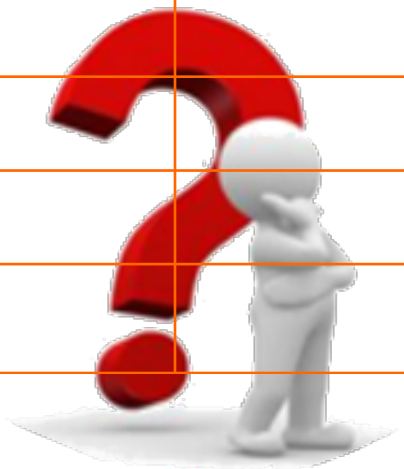
Sterile medicinal products	Minimum Acceptable quality of Water
Parenteral	
Ophthalmic	
Haemofiltration Solution	
Peritoneal Dialysis Solutions	
Irrigation Solutions	
Nasal / Ear Preparations	
Cutaneous Preparations	

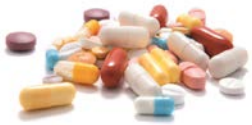


3- Which pharmaceutical water for which process ?

2- Non-Sterile Medicinal Products

Non-sterile medicinal product	Minimum acceptable quality of Water
Oral Preparations	
Nebuliser Solutions	
Cutaneous Preparations	
Nasal / Ear Preparations	
Vagin Rectal / Vaginal Preparations	





3- Which pharmaceutical water for which process ?

3- Water Used During the Manufacture of APIs

Type of manufacture	Product requirements	Minimum acceptable quality of water
Synthesis of all intermediates of **API**s prior to final isolation and purification steps	No requirements for sterility or apyrogenicity in API or the pharmaceutical product in which it will be used	
Fermentation media	No requirements for sterility or apyrogenicity in API or the pharmaceutical product in which it will be used	
Extraction of herbals	No requirements for sterility or apyrogenicity in API or the pharmaceutical product in which it will be used	

3- Which pharmaceutical water for which process ?

3- Water Used During the Manufacture of APIs

Type of manufacture	Product requirements	Minimum acceptable quality of water
Final isolation and purification	No requirements for sterility or apyrogenicity in API or the pharmaceutical product in which it will be used	
Final isolation and purification	**API is not sterile**, but is intended for use in a **sterile, non-parenteral** product	

3- Which pharmaceutical water for which process ?

3- Water Used During the Manufacture of APIs

Type of manufacture	Product requirements	Minimum acceptable quality of water
Final isolation and purification	**API is sterile** and not intended for parenteral use	
Final isolation and purification	**API is not sterile,** but is intended for use in a sterile, parenteral product	
Final isolation and purification	**API is sterile and apyrogenic**	

3- Which pharmaceutical water for which process ?

4- Water Used During Manufacture of Medicinal Products Which Is Not Present in the Final Formulation

Manufacture	Minimum acceptable quality of water
Granulation	
Tablet **coating**	
Used in **formulation** **prior to non-sterile lyophilisation**	
Used in **formulation** **prior** to **sterile lyophilisation**	

3- Which pharmaceutical water for which process ?

5- Water Used for Cleaning / Rinsing of Equipment, Containers and Closures

In general, the final rinse used for equipment, containers/closures should use the same quality of water as used in the final stage of manufacture of the API or used as an excipient in a medicinal product.

Cleaning / Rinsing of Equipment, Containers, Closures	Product type	Minimum acceptable quality of water
Initial rinse	**Intermediates and API**	
Final Rinse	**API**	
Initial rinse including CIP* of equipment, containers and closures, if applicable	**Pharmaceutical products – non sterile**	

3- Which pharmaceutical water for which process ?

5- Water Used for Cleaning / Rinsing of Equipment, Containers and Closures

In general, the final rinse used for equipment, containers/closures should use the same quality of water as used in the final stage of manufacture of the API or used as an excipient in a medicinal product.

Cleaning / Rinsing of Equipment, Containers, Closures	Product type	Minimum acceptable quality of water
Final rinse including CIP* of equipment, containers and closures, if applicable	**Pharmaceutical products – non sterile**	
Initial** rinse **including CIP* of equipment** , containers and closures, **if applicable**	**Sterile products**	

3- Which pharmaceutical water for which process ?

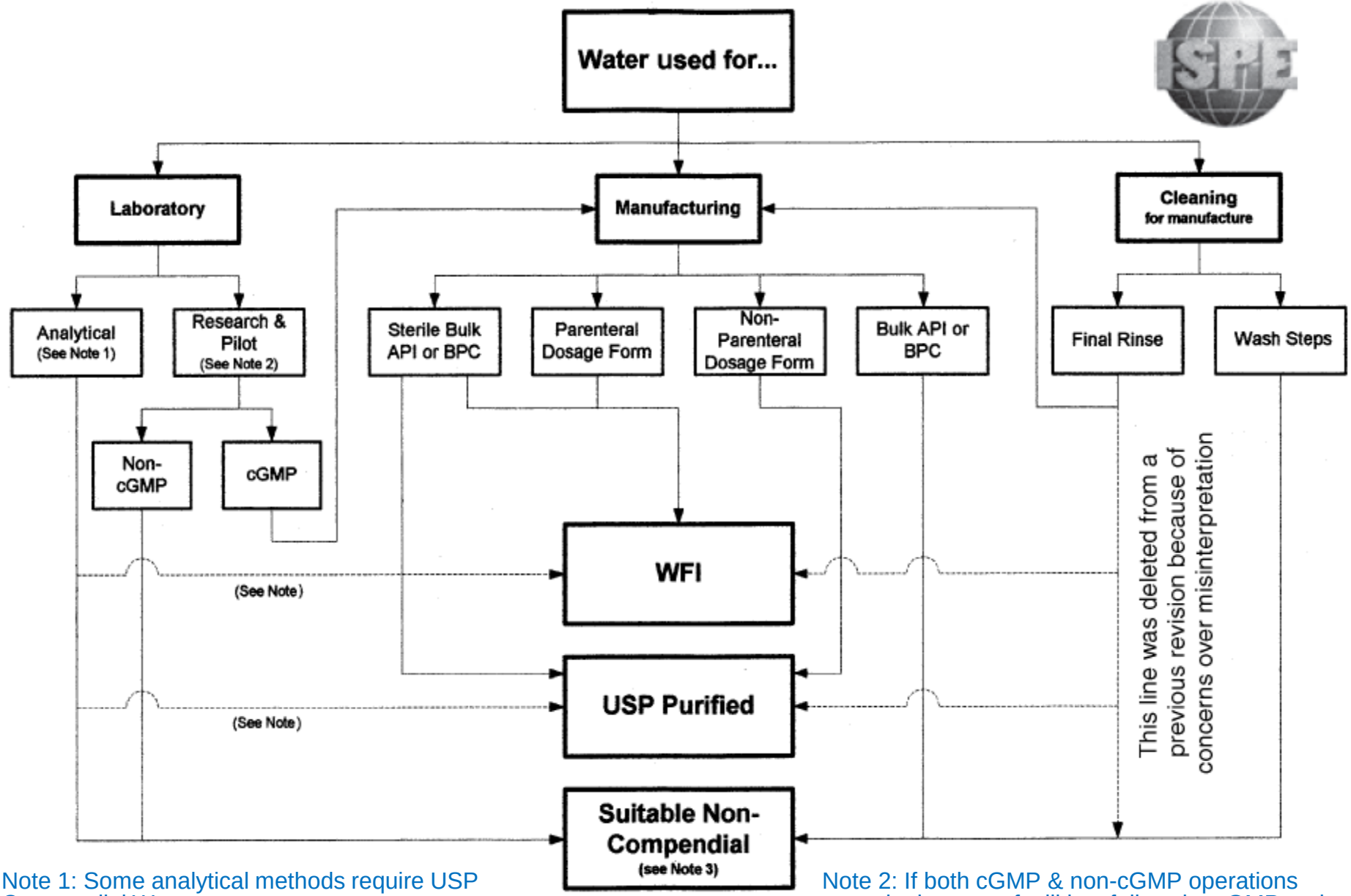
5- Water Used for Cleaning / Rinsing of Equipment, Containers and Closures

In general, the final rinse used for equipment, containers/closures should use the same quality of water as used in the final stage of manufacture of the API or used as an excipient in a medicinal product.

Cleaning / Rinsing of Equipment, Containers, Closures	**Product type**	**Minimum acceptable quality of water**
Final*I** rinse **including CIP* of equipment** , containers and closures, **if applicable**	**Sterile non-parenteral products**	
Final** rinse **including CIP* of equipment** , containers and closures, **if applicable**	**Sterile parenteral products**	

Good Design Practice for GMP Pharmaceutical Facilities, 2005

Pharmaceutical Water Selection



Note 1: Some analytical methods require USP Compendial Waters

Note 2: If both cGMP & non-cGMP operations occur in the same facilities, follow the cGMP path

Table 9-1 Recommended Water Qualities for Process Steps

ISPE vol.6, p127

EUROPEAN ASPECTS

Water for:	Mammalian	Microbial
Fermentation	Purified Water, Highly Purified Water[1], or WFI	Potable Water[6], Process[3], or Purified Water
Harvest/Recovery and Initial Purification	Same water as used for Previous Step[2]	Same water as used for Previous Step[2]
Purification Final	Purified Water[4,5]	
Cleaning First Flush	Potable Water[6] or better	
Cleaning Final Rinse	As used in manufacturing step	

Notes for Table 9-1:

1) Highly Purified Water is compliant with WFI product specification produced and/or distributed by alternative means. However, water must be heat treated to remove viruses.
2) Switch to final water quality at purification step where process is no longer able to remove bioburden or pyrogen contamination.
3) Process water can be prepared by a variety of means from storage of potable water to deionized (DI) or demineralized water.
4) Purified water with endotoxins NMT 0.25 EU/ml and control of specified microorganisms (CPMP/QWP/158/01, May 2002).
5) Lower quality water may be used as appropriate for final dosage form.
6) Potable (drinking) water as defined by local rules. It must be monitored and controlled to a defined quality appropriate for the process.

Part 2 –
Which Technology?

Part 2 – Which Technology?

1. Pretreatment.
2. Treatment.
3. Polishing (Final treatment).
4. Storage tank.
5. Distribution loop.

Part 3 – Sanitary Design (ASME-GMP) of critical equipments

Basic Sanitary Design in 11 points

1. _____ Absence
2. Reynolds number greater than_____
3. Internal Roughness _____
4. Drainability and minimal slope of _____%
5. Minimum amount of G_____, maximum amount of W_____ versus C_____
6. _____ valves between some equipment
7. _____ type connectors
8. _____ design tank
9. _____ pressure
10. _____ temperature
11. _____ velocity

Basic Sanitary Design in 10 points

- Sanitary design of:
- Tanks, pumps, heat exchangers, filter, sprayer

1. Dead-leg: _____ x diam
2. _____& _____ Surfaces
3. _____ Junctions
4. Materials in contact _____ and internal finishes: _____
5. Quick joints & connections : _____
6. Loop Pressure_____

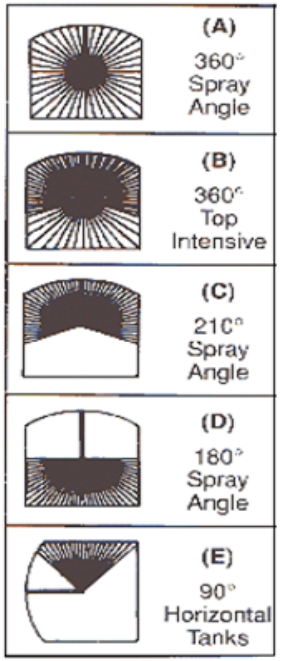
1. Materials compatible with _____ and _____ agents
2. Feed velocity ≥ _____ m/s
3. Loop return velocity≥ _____m/s
4. Loop temperature ≤ ____° C
5. Pressure / Loop ≥
6. Slope ? % _____

Part 4 – Equipment selection

6. Good Engineering Practice (GEP) / Spray balls

Static Sprayballs

Low Pressure – High flow



Advantages:

*No maintenance
*Appropriate spray ball
*Easy to use
*Low mechanical power

Inconvenients:

*High water consumption
*Low mechanical action
*Higher cleaning time

6. GEP / Spray balls

Table SD-5 Flow Rates to Achieve 5 ft/sec (1.52 m/s)

Sanitary Tube Size						Pressure
O.D.		I.D.		Flow Rate		
in.	mm	in.	mm	gpm	Lpm	(Bars)
0.5	12.7	0.37	9.4	1.7	6.3	-
0.75	19.1	0.62	15.7	4.7	18	-
1.0	25.4	0.87	22.1	9.3	35	-
1.5	38.1	1.37	34.8	23	87	-
2	50.8	1.87	47.5	42.8	162	-

6. GEP / Spray balls

Rotative Sprayballs

High Pressure – Low flow

Advantages:

*Low water usage
*High mechanical action
*Wide sprayed area

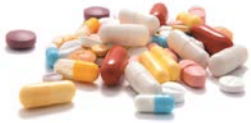
'Turbodisk'

Jets

Slotted

Disadvantages:

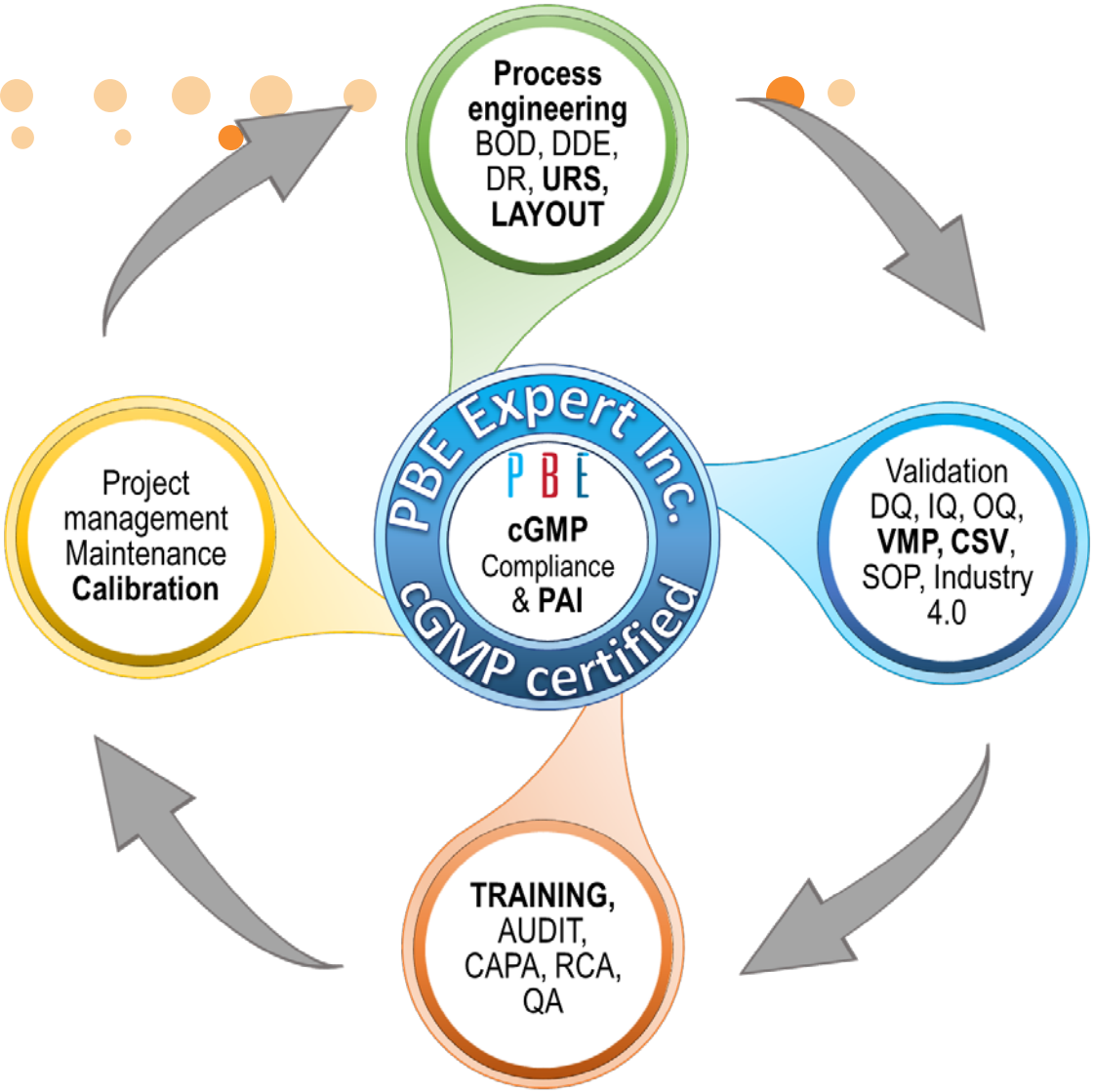
*Higher pump power
*More difficult to use
*Higher maintenance costs



Part 5 – Control and Instrumentation

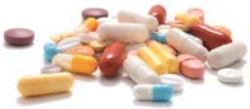
Part 6 – Commissioning FAT, Sat, & IQ, OQ Validation

Part 7 – Quiz - evaluation


Process engineering
BOD, DDE, DR, URS, LAYOUT
Validation
DQ, IQ, OQ, VMP, CSV, SOP, Industry 4.0
TRAINING, AUDIT, CAPA, RCA, QA
Project management
Maintenance
Calibration
PBE Expert Inc.
PBE
cGMP
Compliance
& PAI
cGMP certified

MAPAQ

PBE Expert Inc.
we Process, Build, Engineer



PBE Expert Inc
(Canada) 1.514-616-2692
1.450-600-0790
(Morocco) 212-622-629-224
(Algeria) 213-540-961-234
(Tunisia) 216- 96-751-330
www.pbe-expert.com
pbe@pbe-expert.com
Laval, Canada