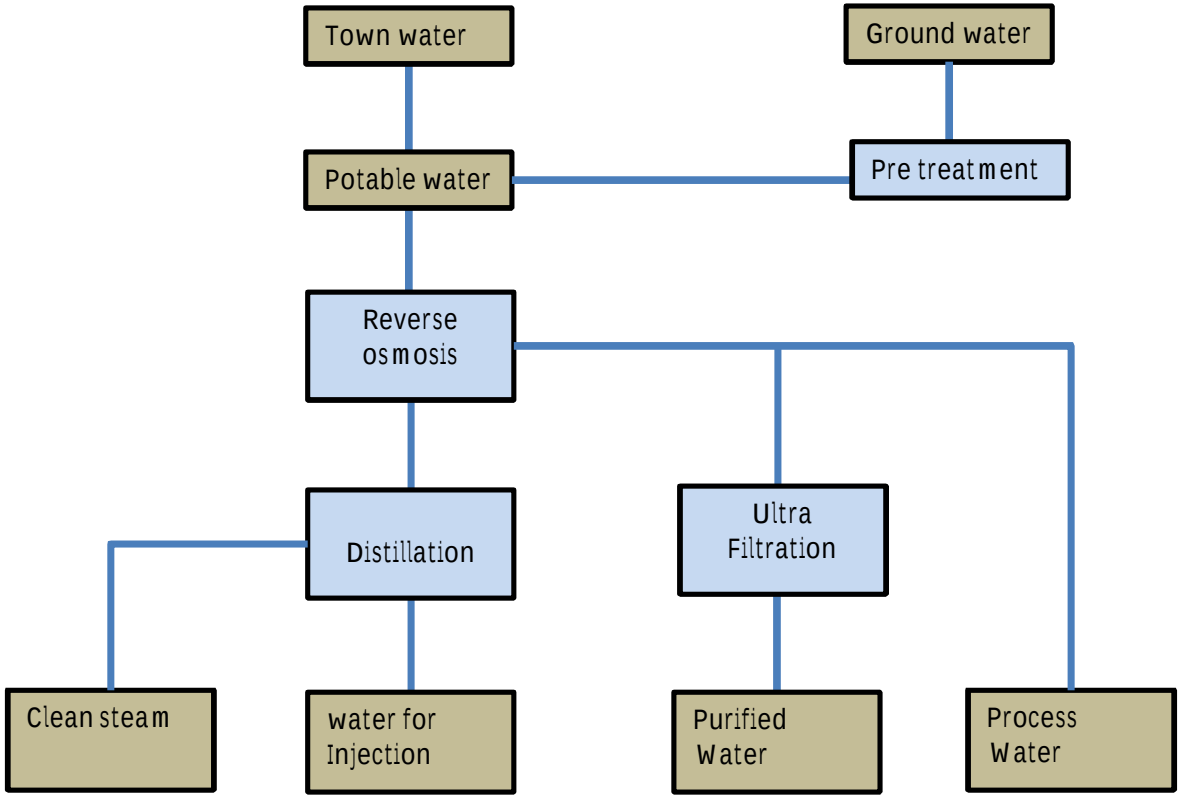
MODULE 6

Qualification of a high purity water system

A water system must be validated and shown to be in a state of control, appropriate samples must be taken from the holding and distribution systems to assess the quality of the water.

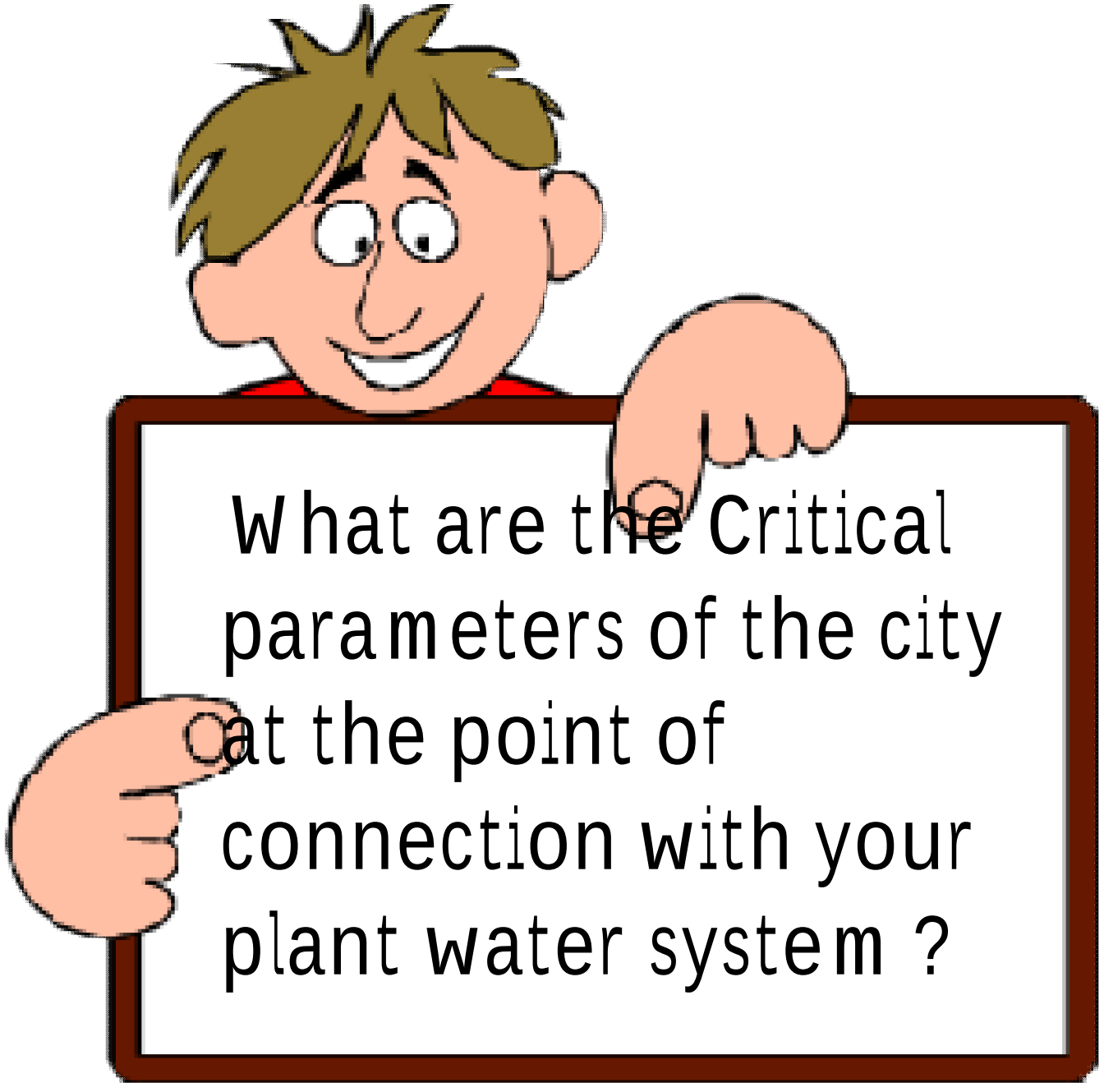
The source of the feed water must meet the local drinking water regulation issued by the government.


Town water
Ground water
Potable water
Pre treatment
Reverse osmosis
Distillation
Ultra Filtration
Clean steam
water for Injection
Purified Water
Process Water

Responsibilities.

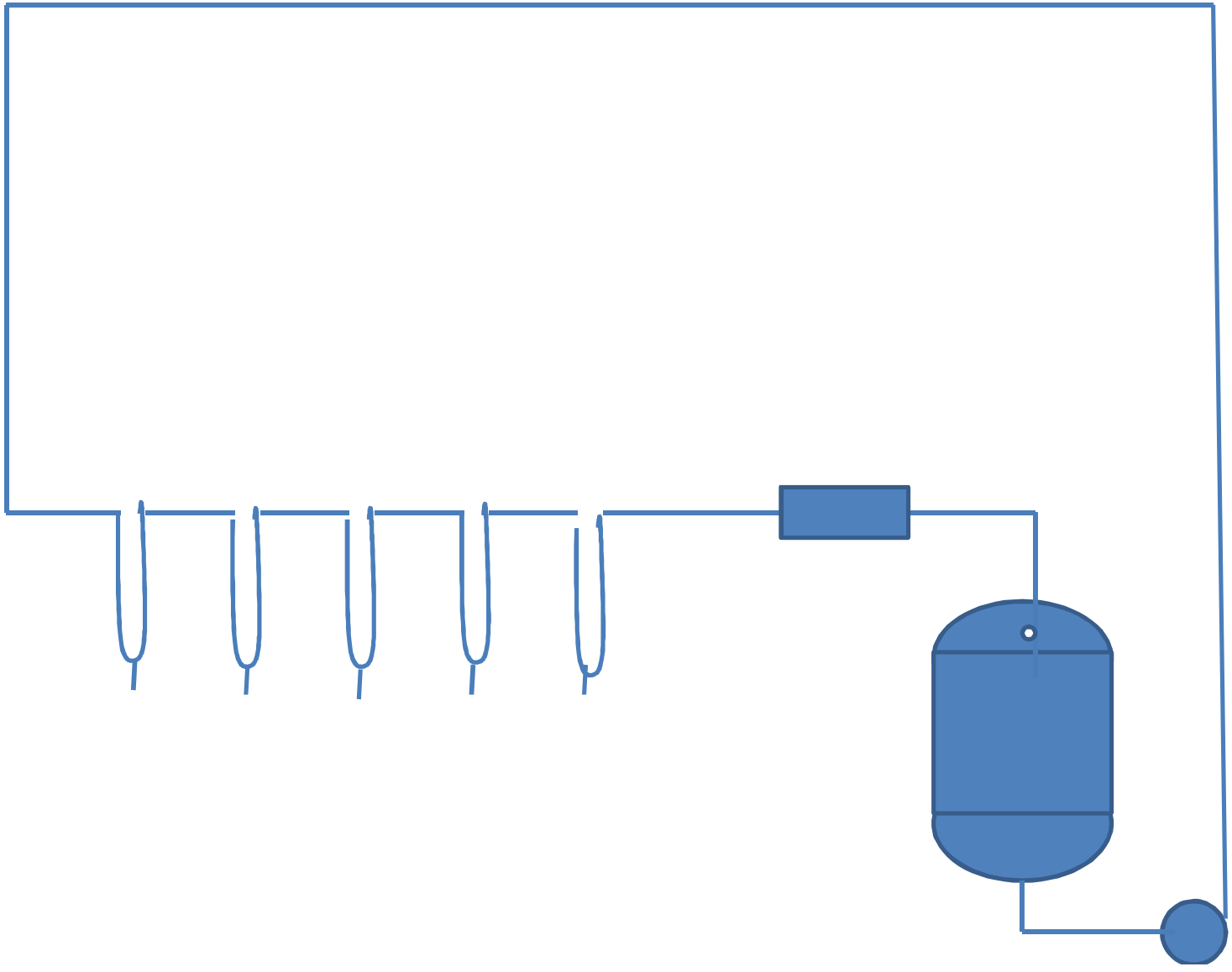
- If the supplied water does not meet the requirements for potable water or if it is above regulation regarding pesticides or other polluants there must be specific testings and treatments included in the qualification steps.

-This must include maintenance, routine controls, procedures and trainings.


What are the Critical parameters of the city at the point of connection with your plant water system ?

Critical parameters

1. Ions : Fe; Al; …
2. Ca; Mg
3. Colloids.
4. Chlorine.
5. Conductivity.
6. Turbidity.
7. Dissolved solids.
8. Dissolved gas : CO2….
9. ….



YOU MUST TELL THE ENGINEERS WHAT IS IMPORTANT FOR YOU.

GOOD ENGINNERING AND QUALITY BY DESIGN WILL ALLOW YOU TO CONTROL, MONITOR, AND GUARANTEE THAT THE QUALITY CONTROL ATTRIBUTES AND PROCESS PARAMETERS ARE ALWAYS WITHIN THEIR ACCEPTANCE CRITERIA

ENABLERS LIKE STATISTIC CONTROL OF THE PARAMETERS WILL PREVENT THE PARAMETERS FROM DRIFTING.


What about qualification and design ?

« Start with the end in mind »

Your will is that you can demonstrate that the qualified and validated system is in the same shape and behaves the same way than when it has been validated (at the end of the PPQ final report).

You, then, must have the possibility to control the critical parameters at the critical location and thus ensure that your process is « fit for purpose ».

Start with the end in mind

Imagine that you are in the future and that the project is already in place.

You will have to maintain the system and thus to monitor and control the critical parameters.

You will have to deal with non conformities.

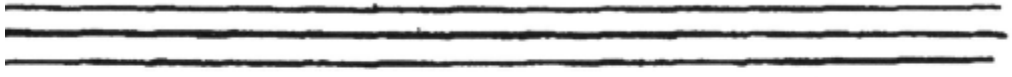
You will also have to make annual review and re-qualification.

This philosophie will drive you through the process of commissioning/process and qualification.

AVOID CONTAMINATIONS

1. REYNOLDS NUMBER HIGH ENOUGH TO ENSURE A TURBULENT FLOW.

$$\mathrm{Re} = \frac{\text{inertial forces}}{\text{viscous forces}} = \frac{\rho \mathbf{v} L}{\mu} = \frac{\mathbf{v} L}{\nu}$$ [8]



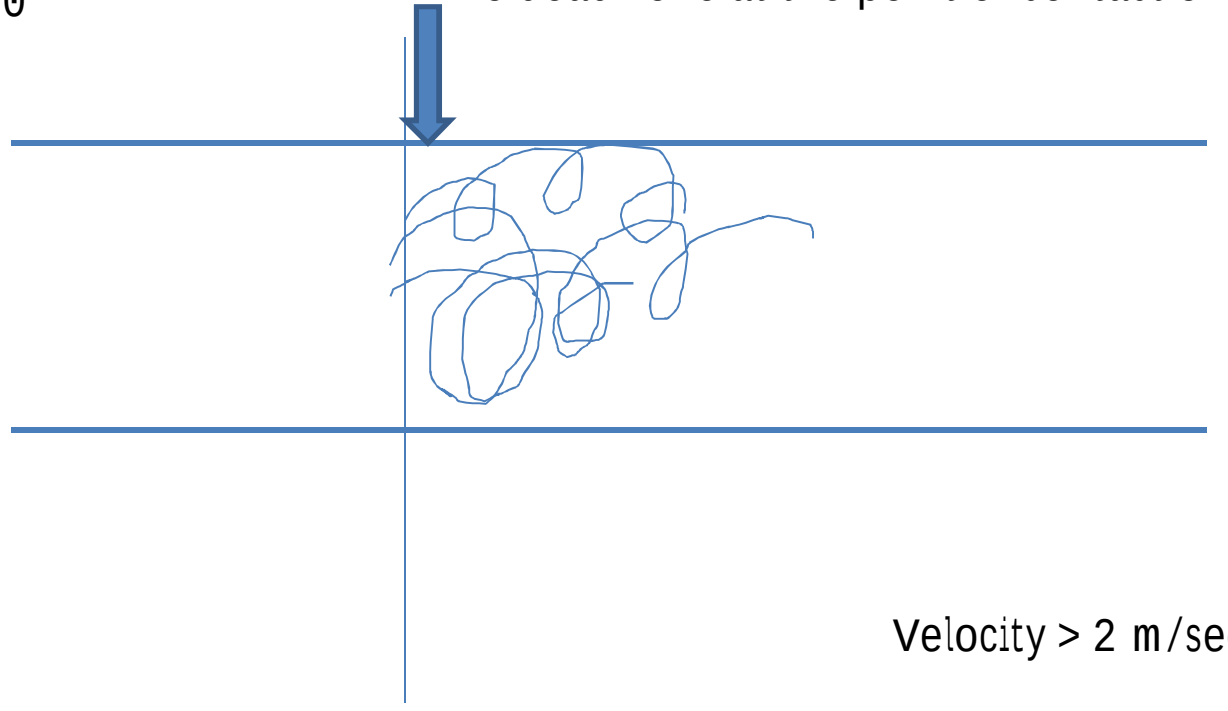
Laminar flow

Turbulent flow

turbulent flow

Re > 3000

No dead zone at the point of contact of the pipe



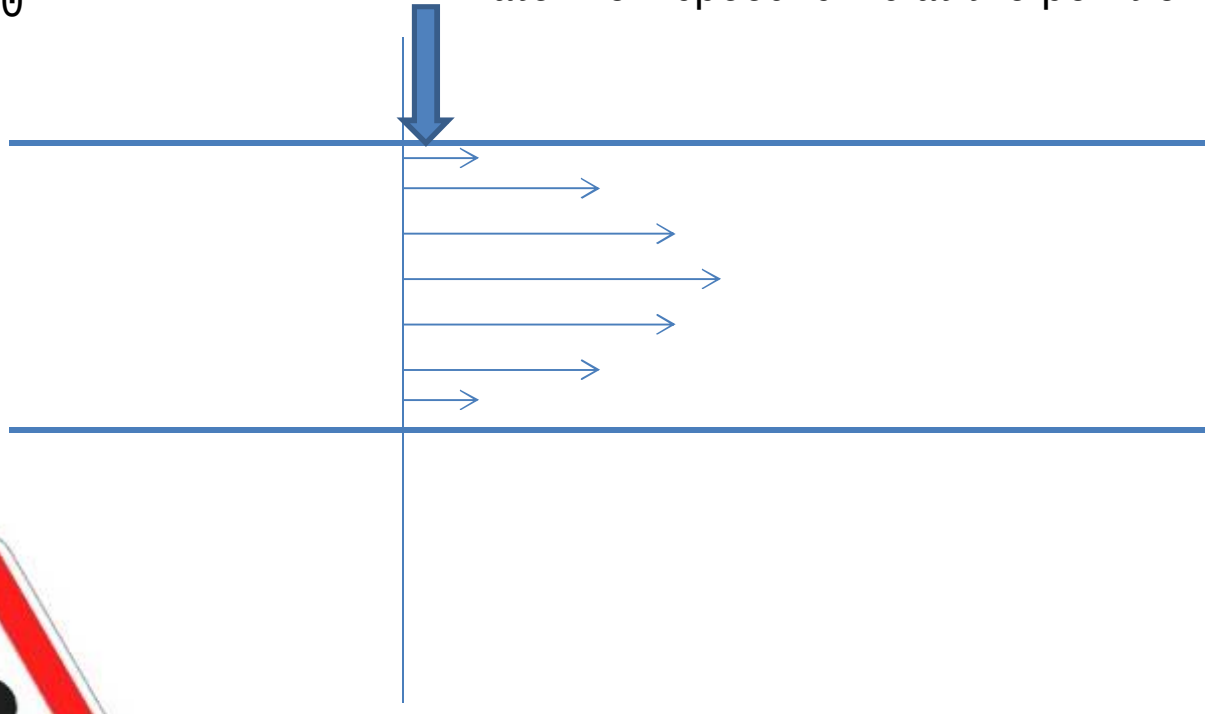
Velocity > 2 m/sec

SAFE DESIGN

Laminar flow

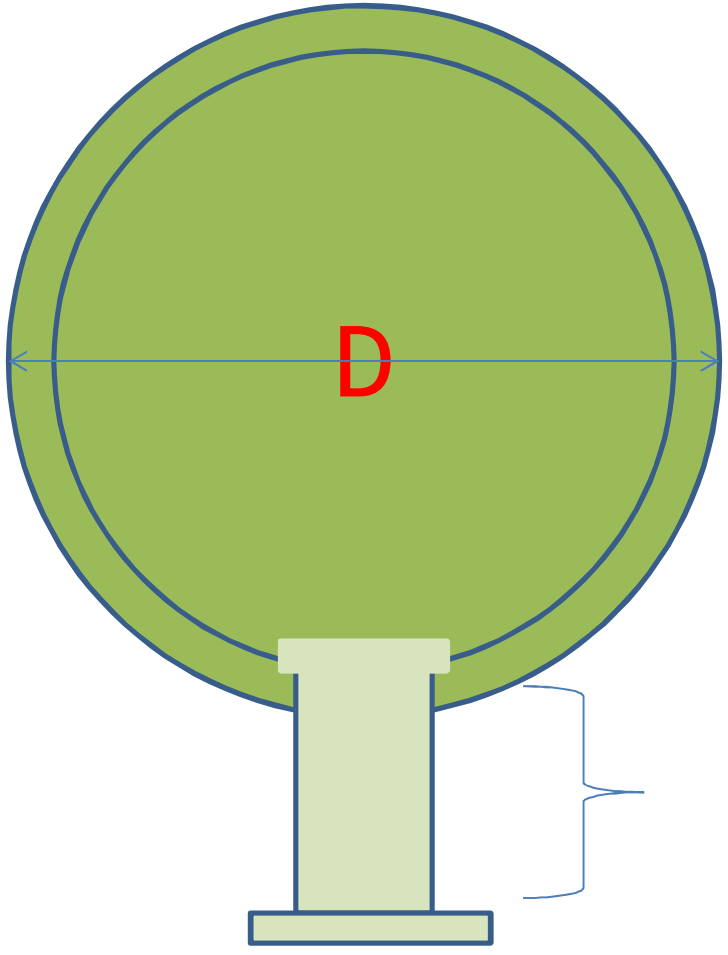
Re < 3200

Water flow speed is = 0 at the point of contact of the pipe



FORMATION OF BIO FILM

3 d RULE



Mini < «3 D

Good engineering design

WRONG DESIGN

GOOD DESIGN

SLOPE 1 TO 2 % RECOMMENDED

SPECIAL ATTENTION TO

1. DEFINITION OF POINT OF USE.
2. DEFINITION OF BATCHES OR CONTINUOUS PRODUCTION.
3. SAMPLING.
4. SANITATION ANS STERILISATION : BEST METHOD ?
5. MATERIAL OF CONSTRUCTION.
6. WELDINGS.
7. MATERIAL CERTIFICATES.
8. COMPOSITION OF STAINLESS STEEL.
9. TRACEABILITY.

SPECIAL ATTENTION TO

1. DATA INTEGRITY.
2. CLEANING OF PIPINS.
3. PASSIVATION OF PIPING.
4. DEFINITION OF CRITICAL PARAMETERS.
5. DEFINITION OF CRITICAL QUALITY ATTRIBUTES.
6. RISK ASSESSMENT.
7. LEACHABLE AND EXTRACTABLES FOR MEMBRANE

SPECIAL ATTENTION TO

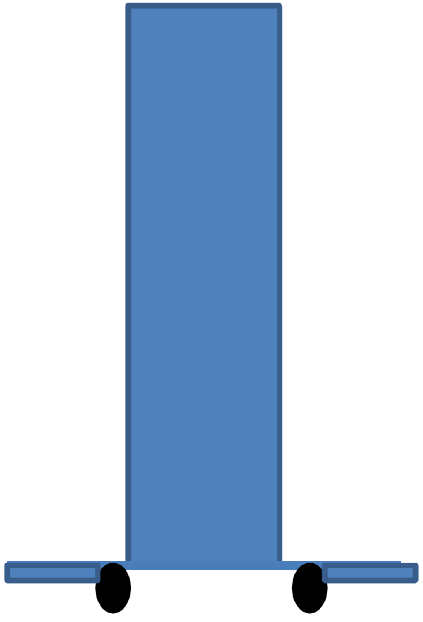
1. MAINTENANCE ACCESS
2. INSTALLATION OF FITTINGS AND VALVES ACCORDING TO RECOMMEDED PROCEDURES
3. LABELING AND TRACEABILITY OF COMPONENTS
4. DROP OF WATER VELOCITY WHEN DEMAND OF WATER AT ONE OR MORE USER POINTS .
5. FINISHING : ELECTROPOLISH > 0.8 µm

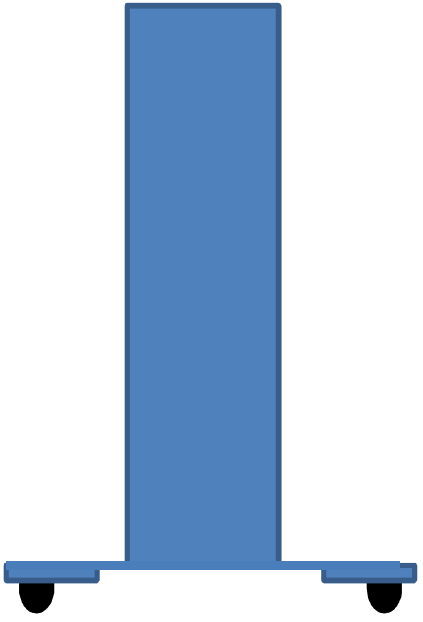
SPECIAL ATTENTION TO

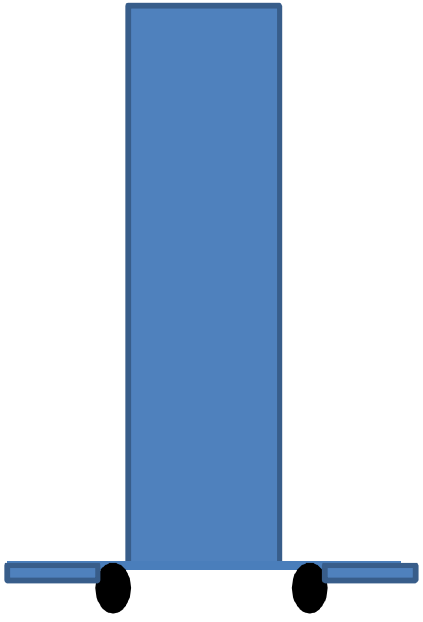
1. STORAGE TANKS WITH 0.2 µm VENT FILTERS.
2. SPRAY BALLS IN THE STORAGE TANK
3. SiC/SiC MECHANICAL SEALS STERILISABLE.
4. LEVEL CONTROL WITH ALARMS.
5. HEAT EXCHANGER TUBES TYPES NOT PLATE HEAT EXCHANGERS.
6. MONITOR CRITICAL PARAMETERS : FLOW, TEMPERATURE, PRESSURE, TOC, CONDUCTIVITY.
7. RISK ASSESSMENT TO DEFINE THE MEASURING TOLERANCES.

SPECIAL ATTENTION TO

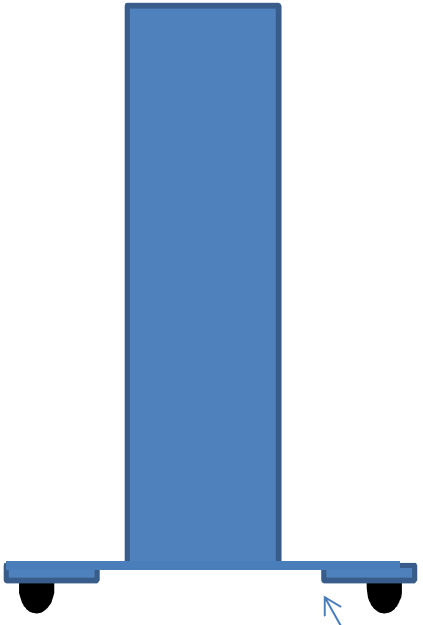
1. VIOLATION OF INTEGRITY IF THE LOOP IS OPEN.
2. PRESSURE RELIEF DEVICES : RELIEF VALVES VS RUPTURE DISKS.
3. QUALITY OF GASKETS.
4. QUALITY OF FITTINGS.







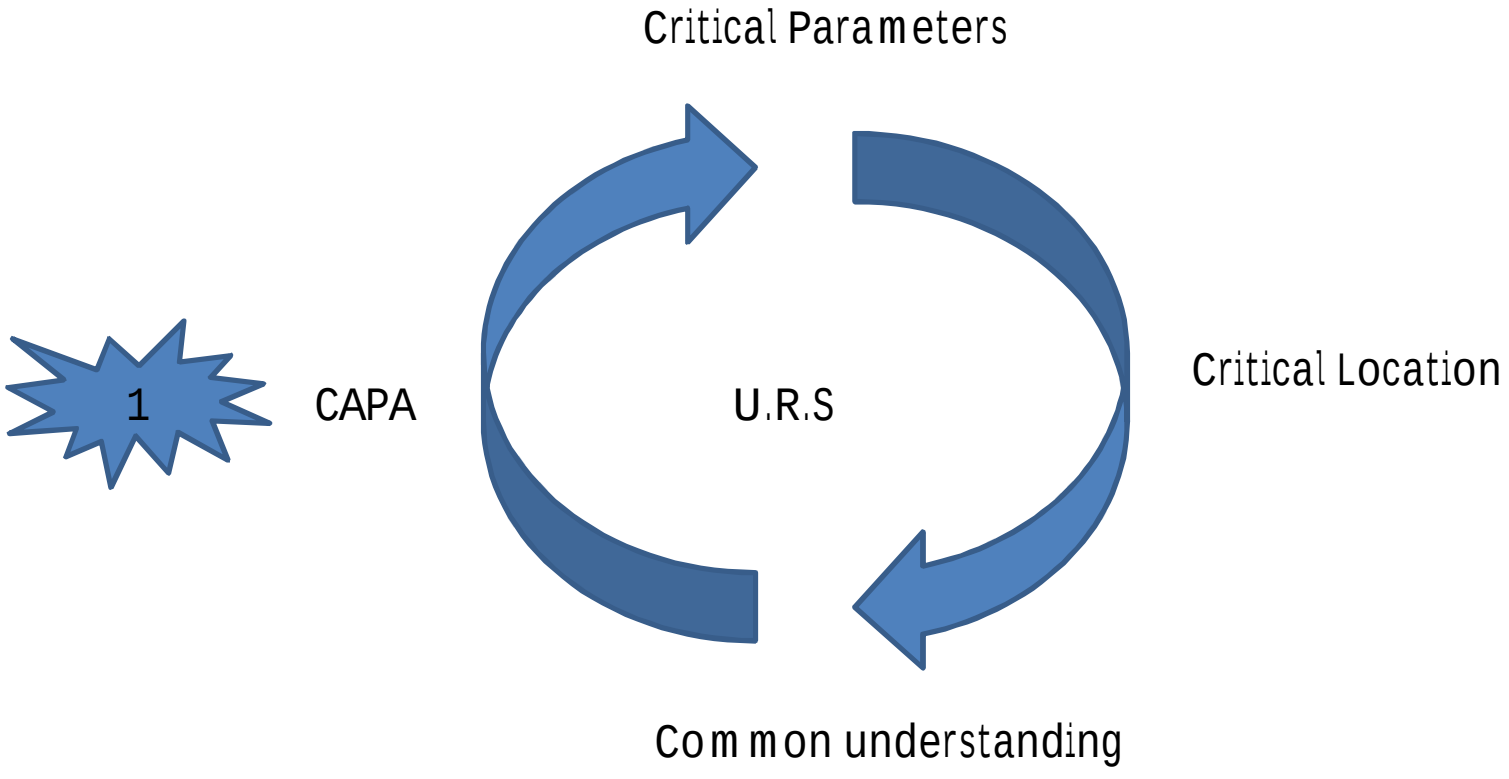
YES



NO

RETENTION
BIOFILM

Start with the end in mind



CAPA

Corrective and preventive action are improvements to eliminate causes of non conformity or other undesirable situations

Corrective action is a reaction to any of the cause

Preventive action is any proactive methodology used to determine *potential* discrepancies

Differences between correction, corrective action and preventive action

Correction

Put fire out
(at the time)

Corrective Action

What caused fire
and how to prevent
recurrence
(after event)

Preventive Action

Stop fire from
happening
(before event)

On which parameters do I want to have control on ?

1. Examine endotoxins.
2. Examine water chemistry.
3. Examine bioburden
4. Review efficacity of sanitation procedures and schedule.
5. Inspect system preventive maintenance records.
6. Verify integrity of sample collection.
7. Verify SOP
8. Inspect systems dead legs, proper sloping, proper sample port design and location.
9. Evaluate impact upon processed components.

This will define the systems that you want to control

1. Examine endotoxins.
2. Examine water chemistry.
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How do I control ?
Where to control ?
How often ?

Link the systems to the parameters ....

System	Parameters
1. Endotoxins.	1. Level of Endotoxins.
2. Water chemistry.	2. Conductivity, PH,....
3. Bioburden	3. CFU
4. Sanitation procedures.	4. F0; T; time
5. Sample collection.	5. Volume of water

Link the systems to the parameters ....

System	Parameters
1. Hardware	1. QMS
2. Dead legs,	2. Weldings
3. Proper sloping,	3. Isometrics,
4. Proper sample port design	4. I.Q protocol,
5. location.	5. Design qualification
6. Evaluate impact.	6. User points.

Link the parameters to the functions....

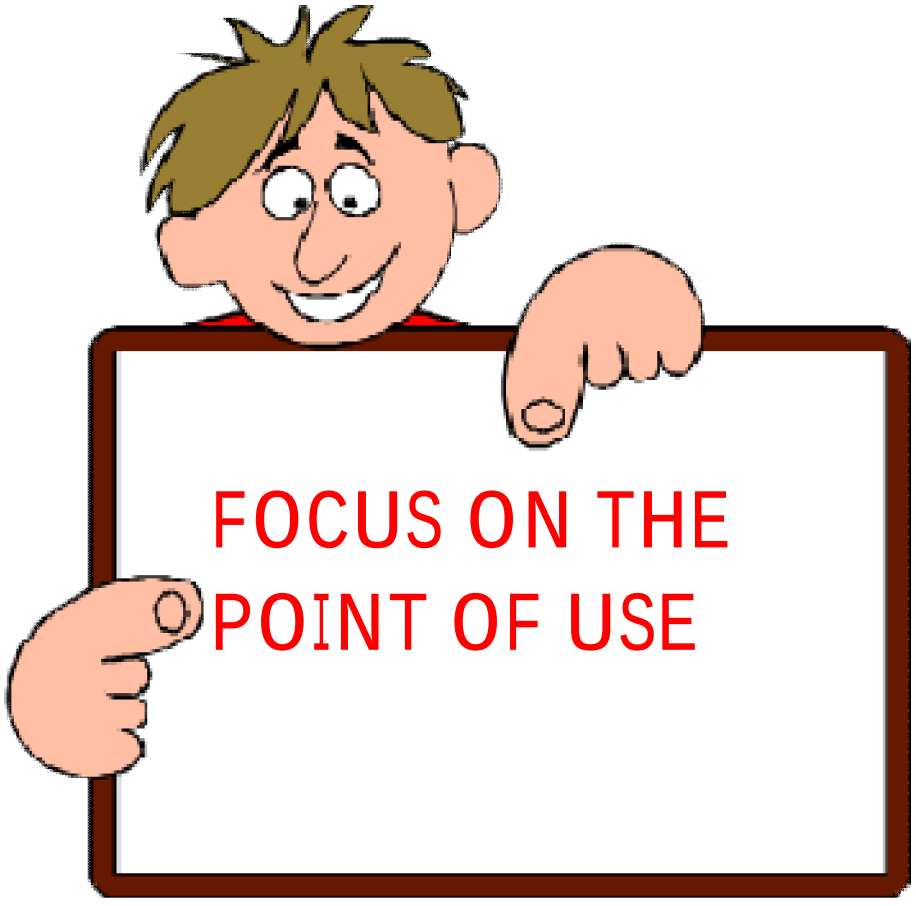
Parameters		Functions
1. Level of Endotoxins.	→	1. Sampling.
2. Pharmacopeia.		2. Sampling
3. Pharmacopeia		3. Sampling
4. F0; T; time		4. Probes, PLC, Software, harware
5. Data Integrity.		5. SOPs, audits
6. Design.		6. Design reviews

Link the parameters to the functions....

Parameters		Functions
1. QMS	→	1. QMS and VMP
2. Weldings		2. IQ
3. Isometrics,		3. Isometrics review,
4. I.Q protocol,		4. I.Q protocol,
5. Design qualification		5. Design qualification
6. User points.		6. User points review.
7. Risk assessment.		7. Risk analysis on potential patient impact.

User requirements VS sampling sites :

Systems	Location
1. Filling line	1. Open container
2. Room air	2. Work area
3. Water	3. Point of use
4. Surface	4. Stopper bowl
5. Compressed air	5. Farthest point
6. LAF	6. Place of Activity

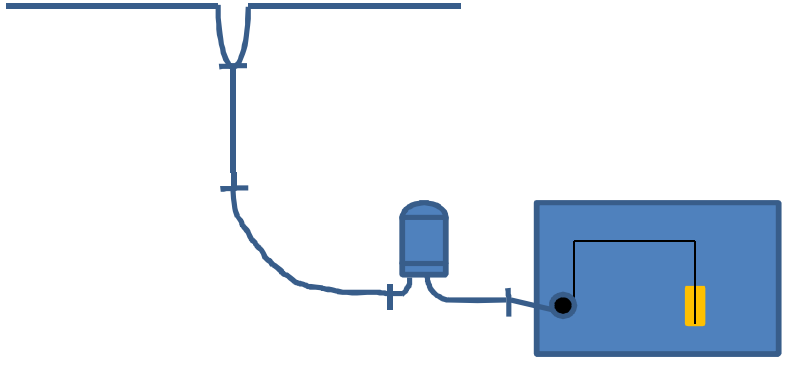

FOCUS ON THE
POINT OF USE

IT IS A GOOD EXAMPLE TO FOCUS ON THE DEFINITION OF THE POINT OF USE AS ENGINEERS CANNOT GUESS YOUR DEFINITION OF THE POINT OF USE.

YOU WILL HAVE TO HELP THEM

IN THE FOLLOWING PROCESS FLOW DIAGRAM.

WHERE IS THE POINT OF USE ?

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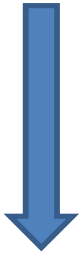
DISCUSSION BY
GROUP

Where is the point of use ?



Risk analysis