WFI – New Ph Eur Selecting the best production option

Gordon Farquharson, July 2016

National GMP & Validation Forum

Hosted by PharmOut

The new WFI Monograph (0169)

Water for injections in bulk

PRODUCTION

Water for injections in bulk is obtained from water that complies with the regulations on water intended for human consumption laid down by the competent authority or from purified water.

It is produced either:

-by distillation in an apparatus of which the parts in contact with the water are of neutral glass, quartz or a suitable metal and which is fitted with an effective device to prevent the entrainment of droplets; the first portion of the distillate obtained when the apparatus begins to function is discarded and the distillate is collected; or

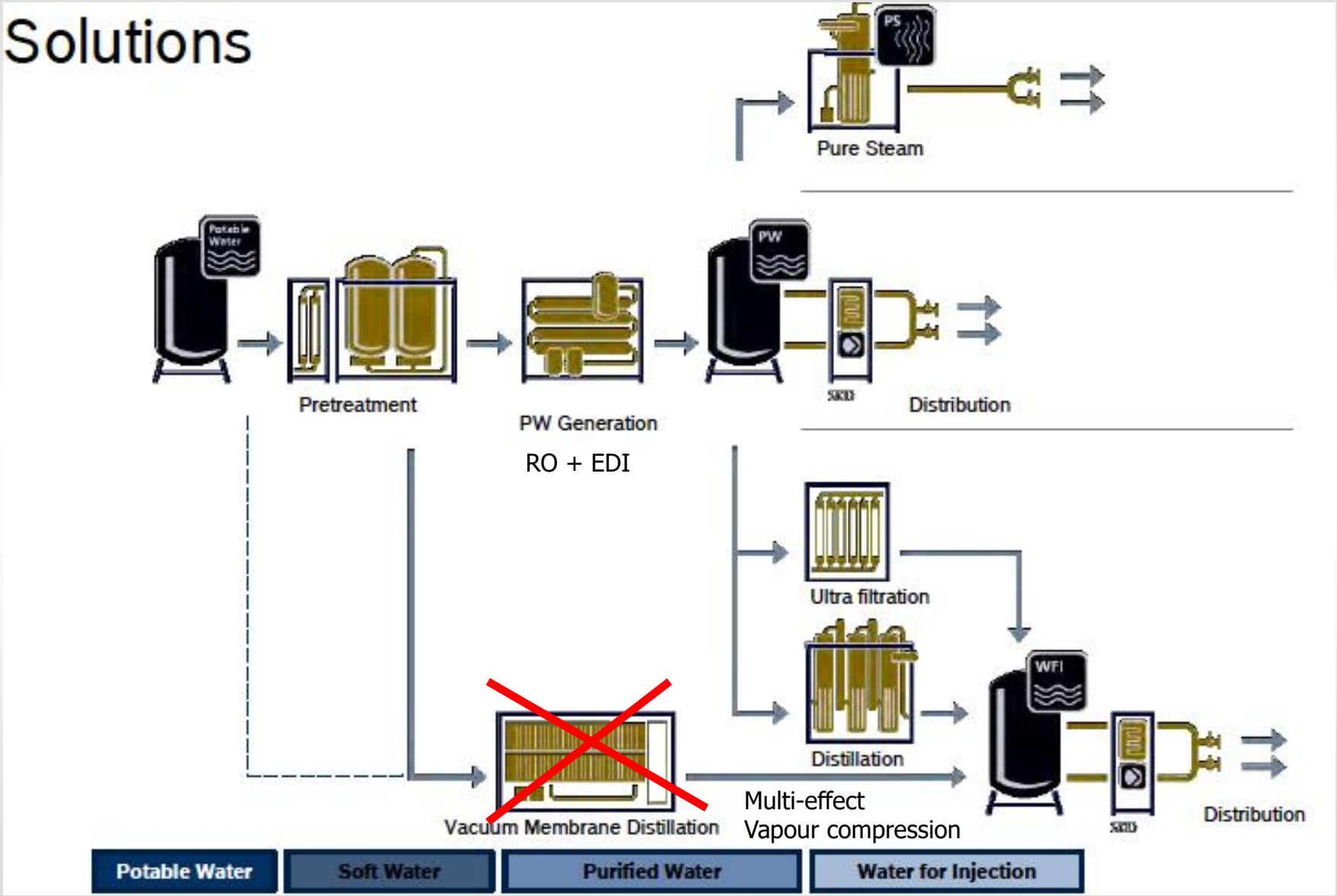
-by reverse osmosis, which may be single-pass or double-pass, coupled with other suitable techniques such as deionisation and/or ultrafiltration.

Correct operation monitoring and maintenance of the system are essential.

In order to ensure the appropriate quality of the water, validated procedures, in-process monitoring of the electrical conductivity, and regular total organic carbon and microbial monitoring are applied.

So now we can see the available WFI production options in Ph Eur

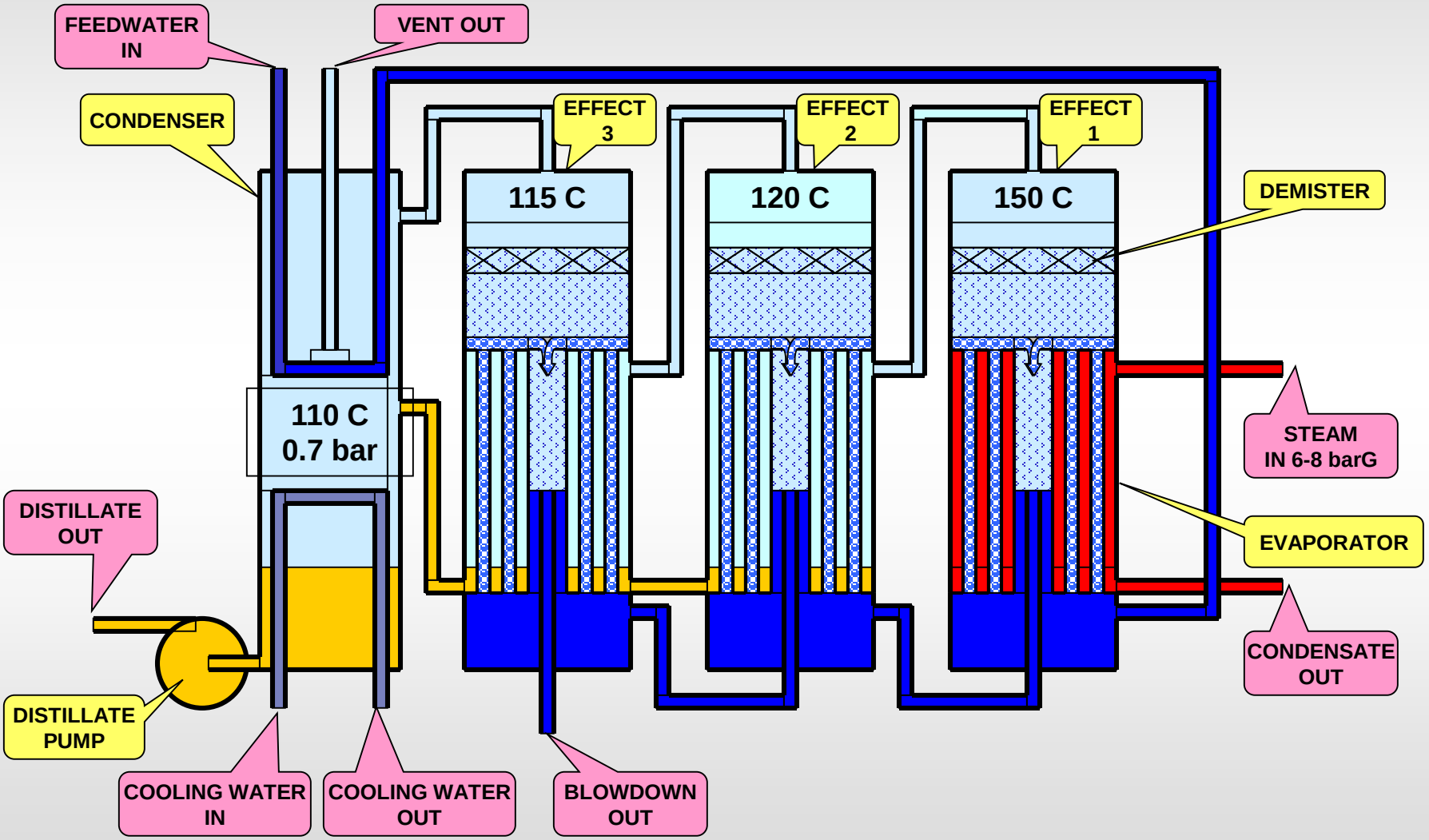
WFI - So what is IN and OUT?



Most common options available - WFI

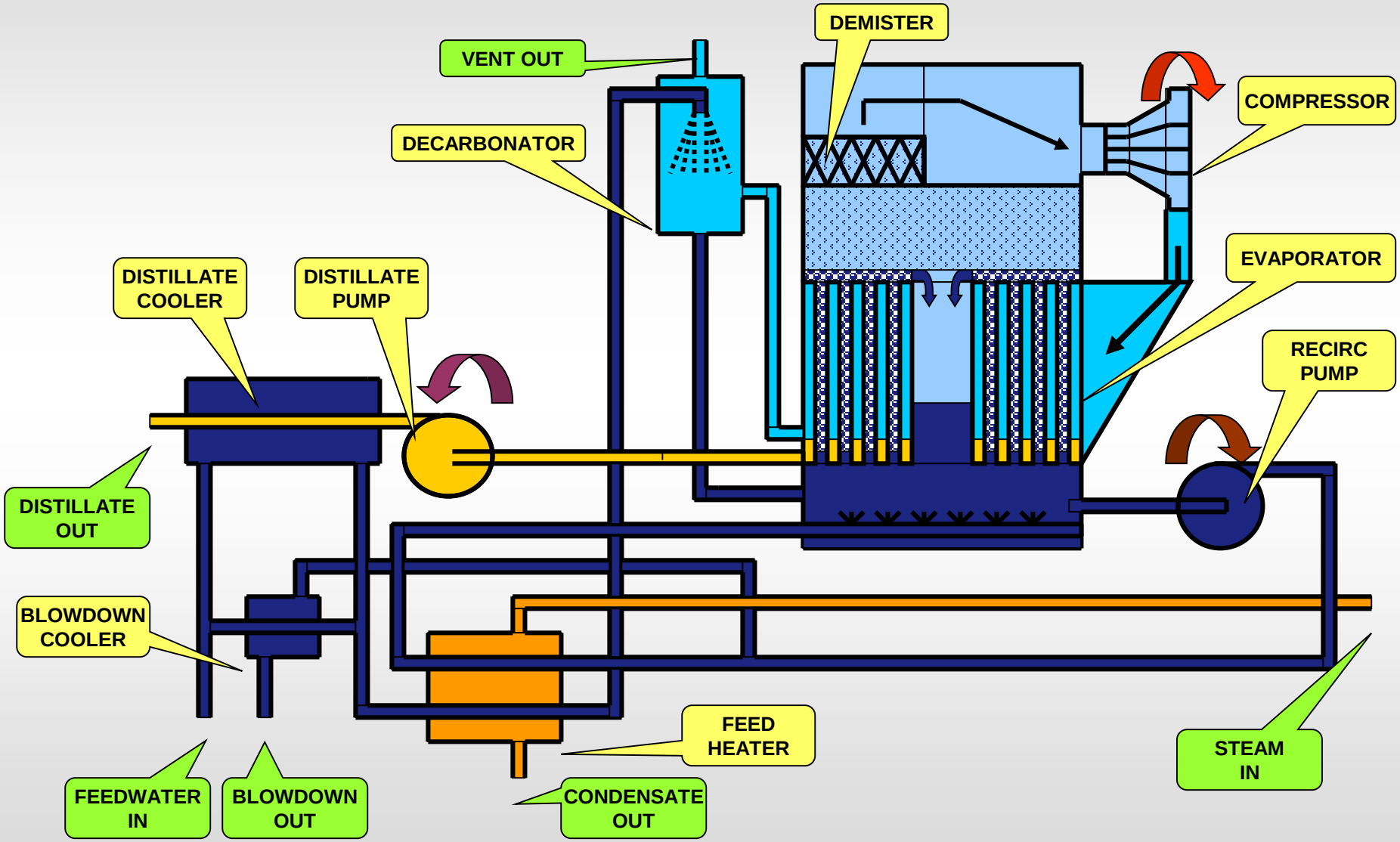
Make it	Store it	Circulate it	Use it
ME Distillation 80 degC	80 degC	80 degC	80 degC
VC Distillation 40 degC	20 degC Micro control periodic thermal Or 80 degC	20 degC Micro control periodic thermal Or 80 degC	20 degC Or 80 degC
RO + DI + UF 20 degC Micro control periodic thermal	20 degC Micro control periodic thermal or Ozone	20 degC Micro control periodic thermal or Ozone	20 degC

Multiple Effect Distillation



Vapour compression distillation

Vapour Compression Distillation



Distillation Options
Some Specific Differences

Multi-Effect

Feed water needs to be close to purified water

Cooling water is required

Separate condenser is used

No compressor required

Distillate and blowdown pumps usually not required

Plant steam @ 6-8 barg

Electrical requirements are minimal

ASME coded pressure vessels

Vapor Compression

Feed water deionised

No cooling water required

No separate condenser

Compressor is required

Distillate and blowdown pumps are required

Plant steam at 2.4-3.1 barg

More electrical requirements for compressor drive

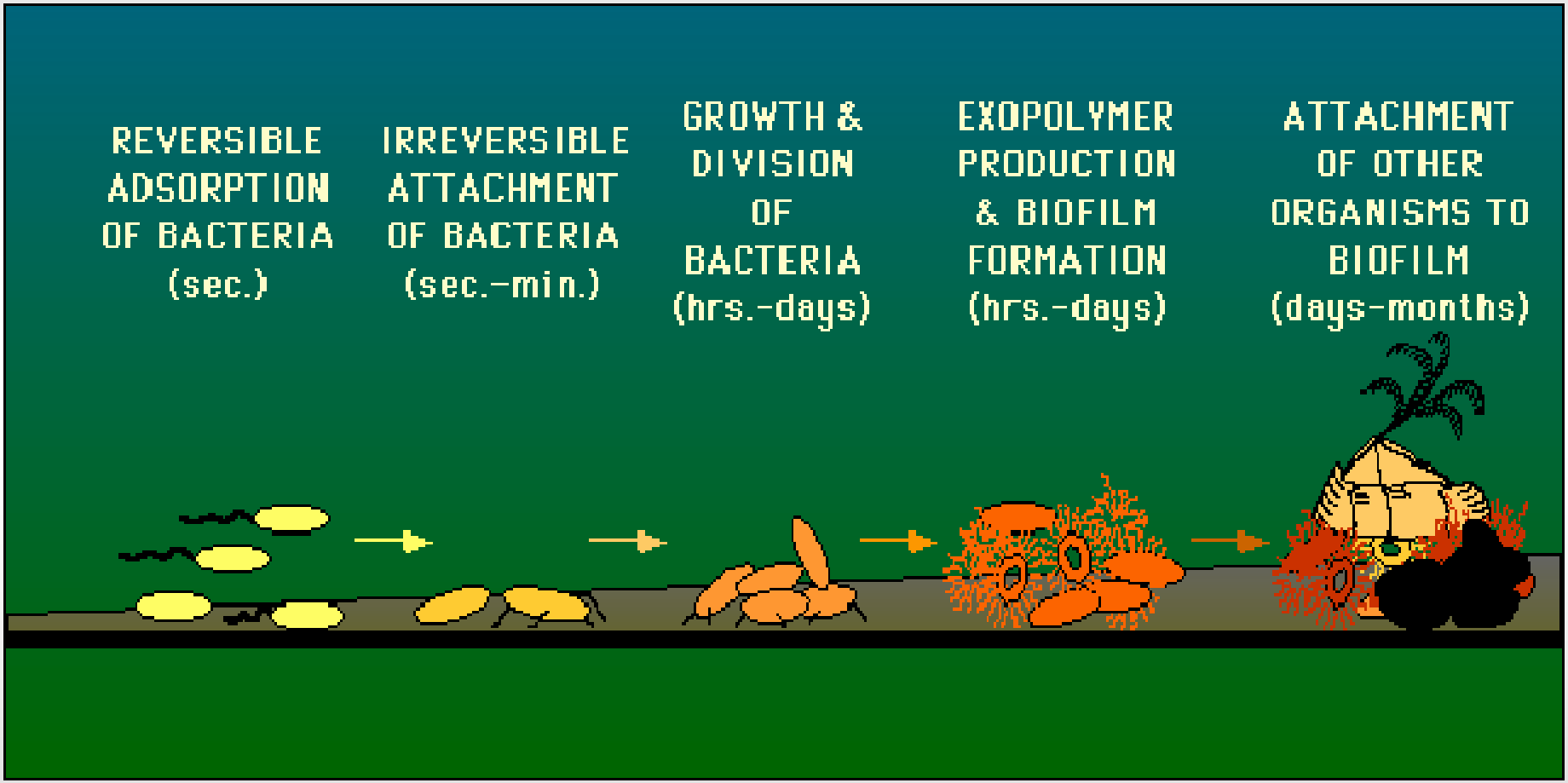
Not a ASME coded vessel

Skid Mounted HPV & WFI Water Generator

- Typical unit purification steps (all capable of thermal sanitisation):
  - Softening.
  - Chlorine removal.
  - Reverse osmosis.
  - Continuous Electro-deionisation.
  - Ultra-filtration

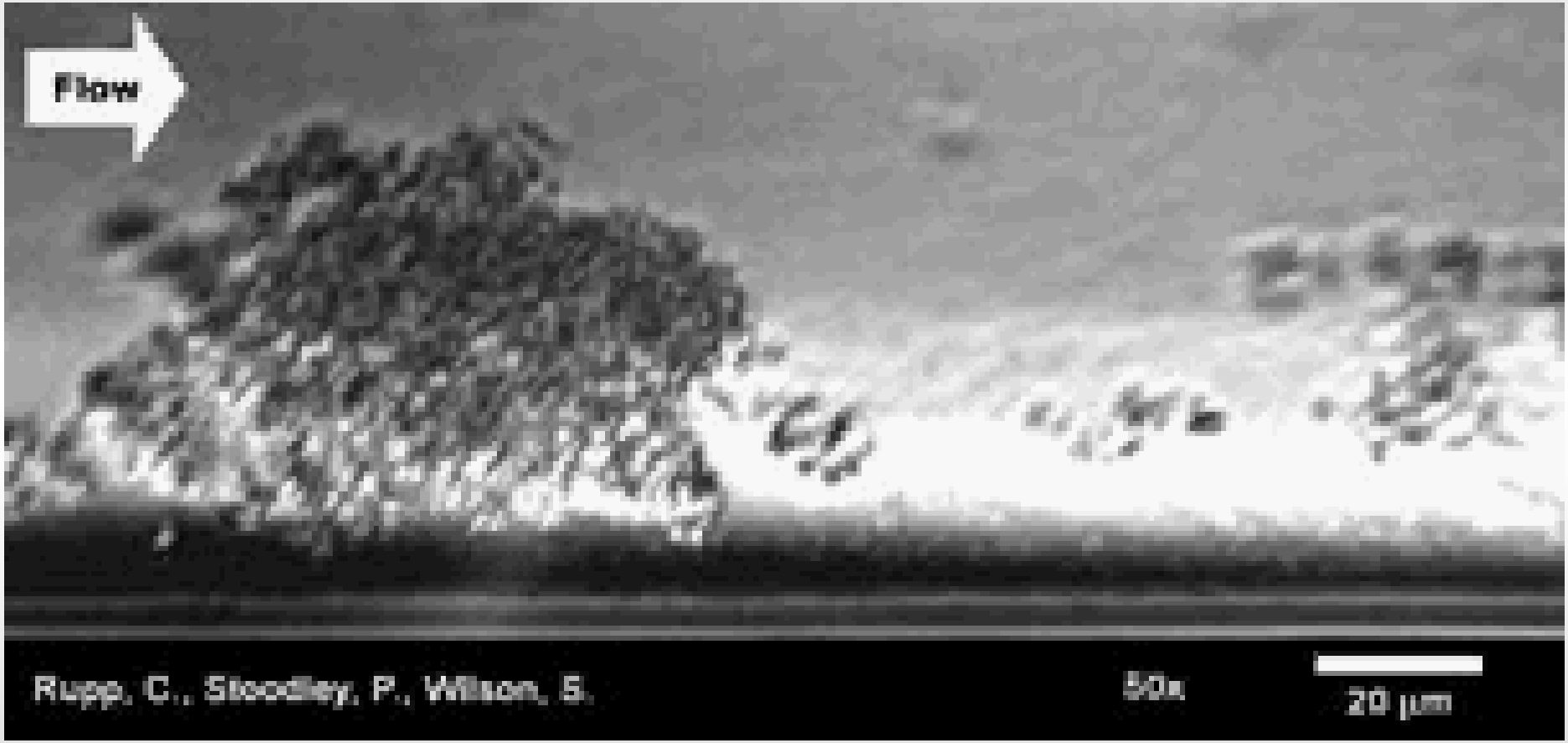
Biofilm and the microbial contamination risk

Biofilm Formation



Mark Wiencek, Rohm & Haas Company, Spring House, PA 19477

Biofilms Can Shed In Water Flow



Making the decision about system selection.

Choosing the best option for you.

Risk & Opportunities – Choosing the best option

- Some use of risk and option assessment.
- The application:
  - WFI for a parenteral dosage form formulation will be considered more critical than WFI for a biotech buffer, media, or elluent.
- Many judgements qualitative:
  - USP → equivalent or better purification capability
  - Reliability (some data (& confidence) from semi-conductor industry)
  - QA and Regulatory confidence/risk. Regulators and B2B.
  - Qualification burden
- Some quantitative
  - Capital cost
  - Running cost – energy & maintenance
  - Carbon liberation

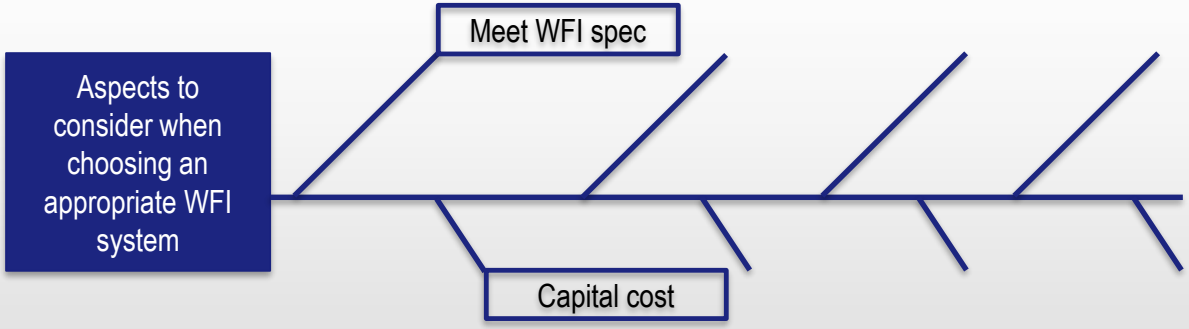
Some aspects to consider

- Ability to deliver water to the required quality specification.
- Ph Eur and GMP compliance.
- Reliability & robustness of system.
  - Not just the purification……..
  - Includes purification, storage and distribution.
- QC cost....
  - Testing.
  - Likely frequency and cost of deviations.
- Capital cost.
- Running cost.
- Availability of utilities.
- Technical support of equipment and utilities.
- Regulatory & partner firm approvals.

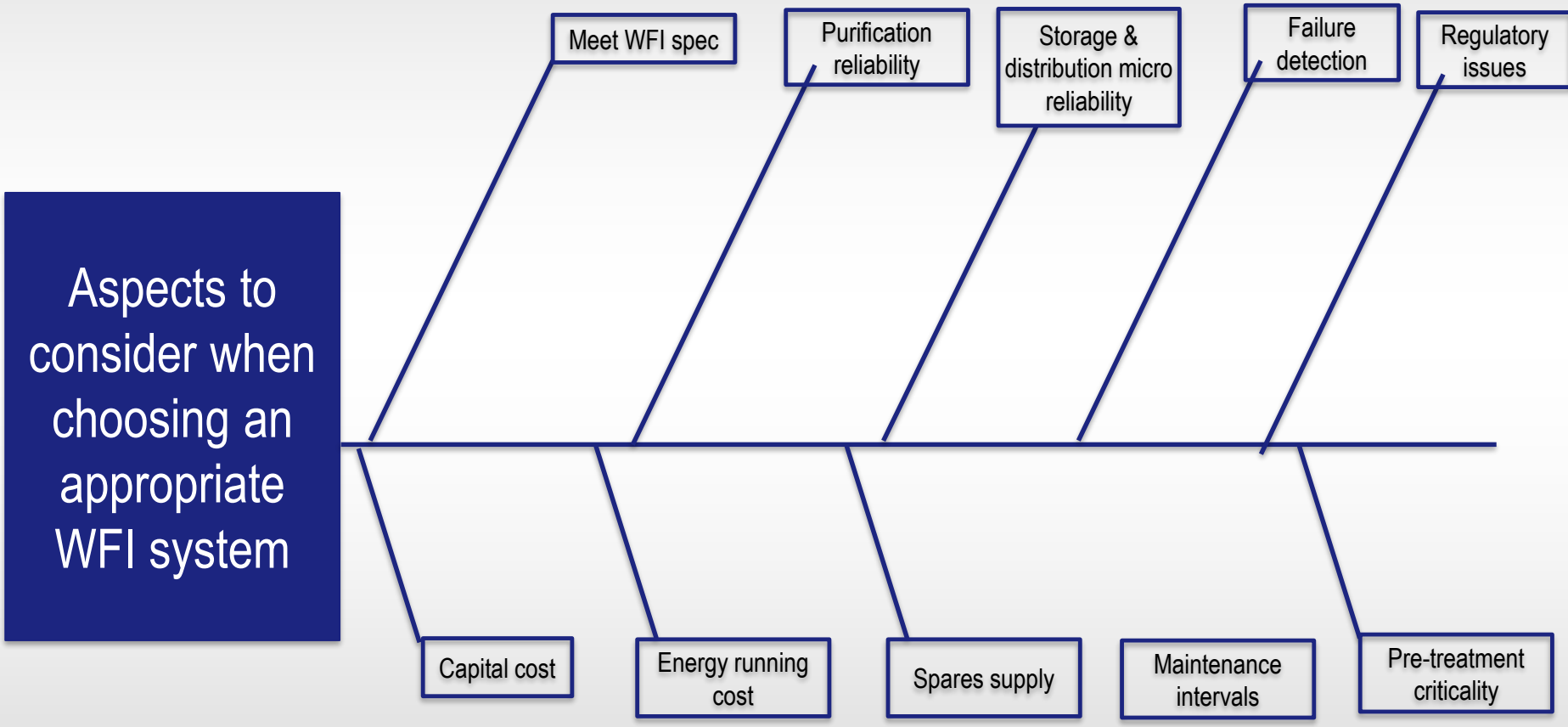
Assessment techniques

Brainstorm aspects to consider

- Suggest Ishikawa (fishbone) diagrams.



Ishikawa example



Kepner Traego analysis - A scoring approach to choosing best option

Example considerations	Multi-effect distillation	Membrane	Vapour compression distillation
Capital cost			
Running cost			
Purification reliability			
Pre-treatment criticality			
Ability to meet water spec			
Micro control in purification			
Micro control in storage and distribution			
Total			

Filling in the scores

Example considerations	Multi-effect distillation	Membrane	Vapour compression distillation
Capital cost	1	3	2
Running cost	1	3	2
Purification reliability	3	1	2
Pre-treatment criticality	1	2	3
Ability to meet water spec	3	3	3
Micro control in purification	3	1	3
Micro control in storage and distribution	3	2	2
Total	15	15	17

Real-time water quality measurement

Real-time on-line water quality

- Today we monitor our systems on-line for
  - TOC
  - Conductivity
  - Temperature, Flow & pressure
- For microbiological purity we still have to rely on Grab-sample testing, and wait 5 days !
- For endotoxin testing we rely on off-line testing.
- Therefore, we alert and alarm deviations immeditaely for some CQAs and after a delay for others.
- Soon we will be able to do better, and it will become GMP & a Pharmacopoeial specification.

Rapid micro methods for water

- In 2014, the first systems hit the market.
- Often called instantaneous microbiological detectors (IMD) or light induced fluorescence (LIF). LIF is a spectroscopic technique capable of high sensitivity in the detection of compounds that fluoresce.
- ‘On-line’ systems Give immediate reading, and Collect samples for typing (traditional methods)
- Very similar to the techniques used for IMD in air.
- Fluorescence is the luminescence that occurs with the absorption of radiation at one wavelength followed by the emission of radiation at a different wavelength.
- Substances that typically fluoresce may be referred to as fluorophores.

Some references

Advances in vapor compression technology for the production of USP WFI. Gsell, Nunez, and Smith-Palmer. ISPE Pharmaceutical Engineering March/April 2013, Vol 33, N0 2.

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EMEA (now EMA): Note for guidance on quality of water for pharmaceutical use. CPMP/QWP/158/01 & EMEA/CVMP/115/01; London May 2002.

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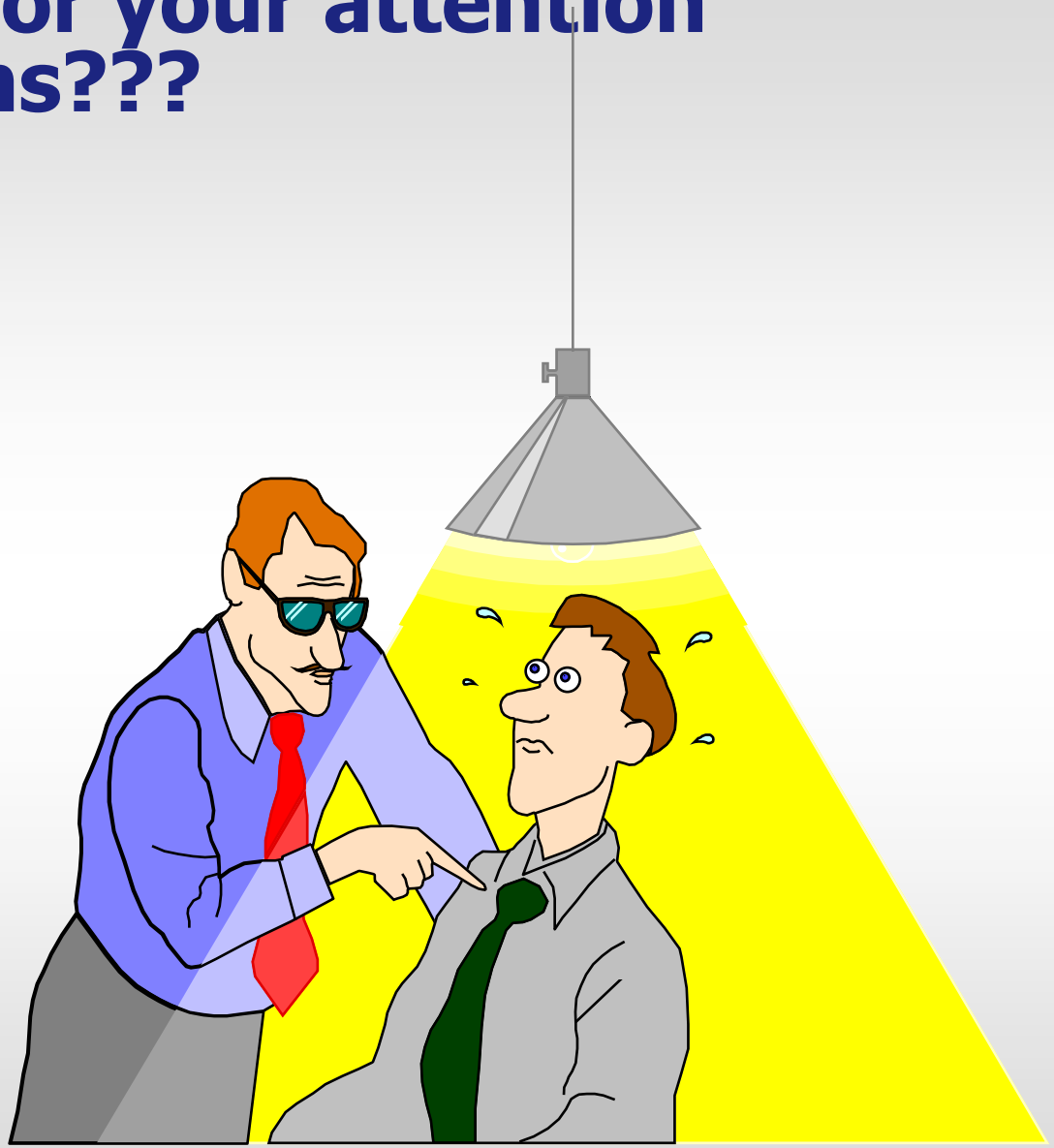
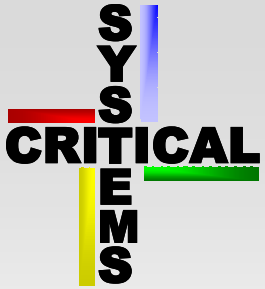
Background document for revision of monograph Water for injections (0169), based on the Reflection Paper endorsed by the European Pharmacopoeia Commission at its 146th Session, June 2013.

Thanks for your attention
Questions???





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