Supplementary Training Modules on Good Manufacturing Practice

Part 4:

Inspection of water purification systems

WHO Technical Report Series No 970, 2012. Annex 2

World Health Organization

Water for Pharmaceutical Use

Objectives

To understand:

- The specific requirements when inspecting water systems, including associated documentation
- Water system inspection techniques and approaches

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Prepare an aide-memoire for items to inspect (1)

May include:

- Schematic drawing review
- Changes to system since installation
- Sampling procedure and plan
- Specifications, results and trends
- Out-of-specification results
- Annual system review
- Deviations

8.

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Prepare an aide-memoire for items to inspect (2)

- Results of system performance monitoring
- Out of limit results, failure investigations and alarms recorded
- Sanitization procedures and records
- Maintenance and repairs logs/records
- Instrument calibration and standardization
- Qualification and validation including DQ, IQ, OQ, PQ
- Requalification when appropriate, etc.

8.

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Where to start:

What is the water to be used for?

- *sterile products*
- *non-sterile products, e.g. oral liquid products, external applications*
- *solid dosage forms*
- *washing and rinsing*

- Start: Document review – site verification – followed by additional document review

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Verification:

- Start with document review (e.g. schematic drawing of the system, "water quality manual" if available, system review)
- Review qualification reports, then change controls (in case of changes – and requalification if appropriate)
- Do on site verification (system in accordance with the drawings, no leaks, calibration etc.)
- Start with source water supply
- Then pre-treatment and treatment systems

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Documentation should reflect information on: (1)

- Pipeline
- Valves (non-return type)
- Breather points
- Couplings
- Pipe slope
- Velocities
- Sampling points
- Drain points
- Instrumentation
- Flow rates

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Documentation should reflect information on: (2)

- Specification for each system element
- Standard procedures for use
- System changes
- Routine and non-routine maintenance
- Investigations and corrective action
- Validation studies
- Chemical and microbiological specifications
- Sampling instructions
- Test procedures
- Responsible persons
- Training requirements

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On site review and verification for raw water

- Storage may be required prior to pre-treatment
- Check material of construction of tank
  - *Concrete, steel are acceptable but check corrosion*
  - *Plastics or plastic linings may leach*
- Check the suitability of the cover
  - *To keep out insects, birds and animals*
- Check disinfection practices

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On site review and verification (e.g. PW):

- Start with source water supply – follow whole system "loop"
- Walk through the system, verifying the parts of the system as indicated in the drawing
- Review SOPs "on site" with the relevant records, logs, results
- Verify components, sensors, instruments
- Inspect the finishing, state, calibration status, labels, pipes, tanks etc as discussed in previous parts of this module

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Water treatment system inspection (1)

- Checks may include:
  - *dead legs*
  - *filters*
  - *pipes and fittings*
  - *Ionic beds*
  - *storage tanks*
  - *by-pass lines*

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Water treatment system inspection (2)

- Checks may include:
  - *pumps*
  - *UV lights*
  - *sample points*
  - *reverse osmosis*
  - *valves*
  - *heat exchangers*
  - *Instruments, controls, gauges, etc.*

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Other checks (1)

- Material of construction
- Weld quality
- Hygienic couplings
- Passivation procedure and records
- Air breaks or “Tundish”

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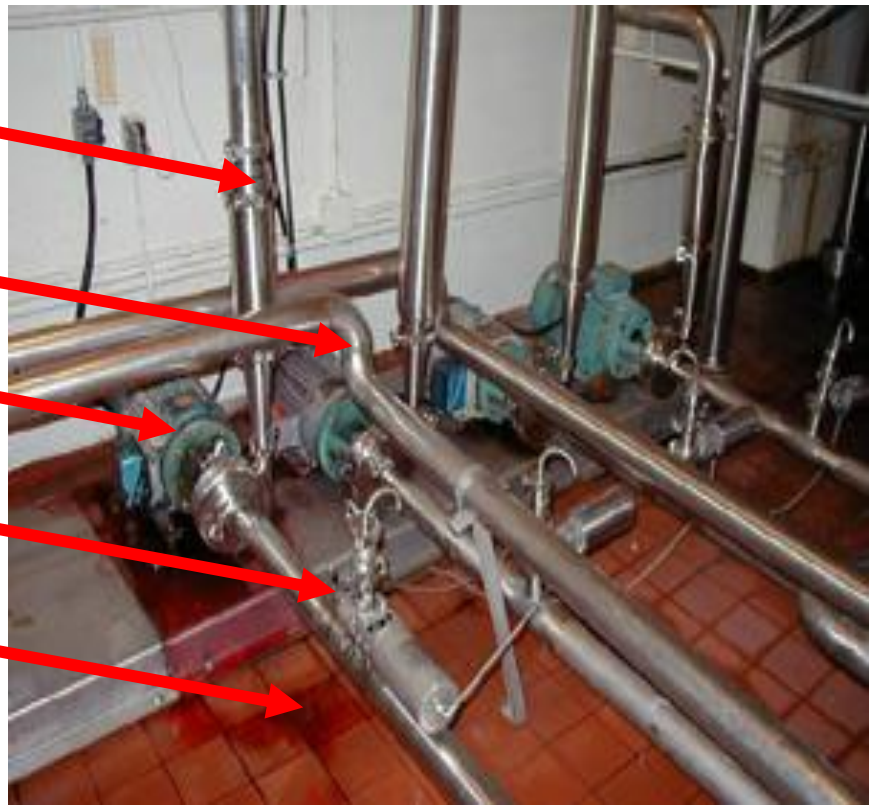
Other checks (2)

Pipes and pumps

- *hygienic couplings*
- *welded pipes*
- *hygienic pumps*
- *hygienic sampling points*
- *acceptable floor*
- *no leaks*



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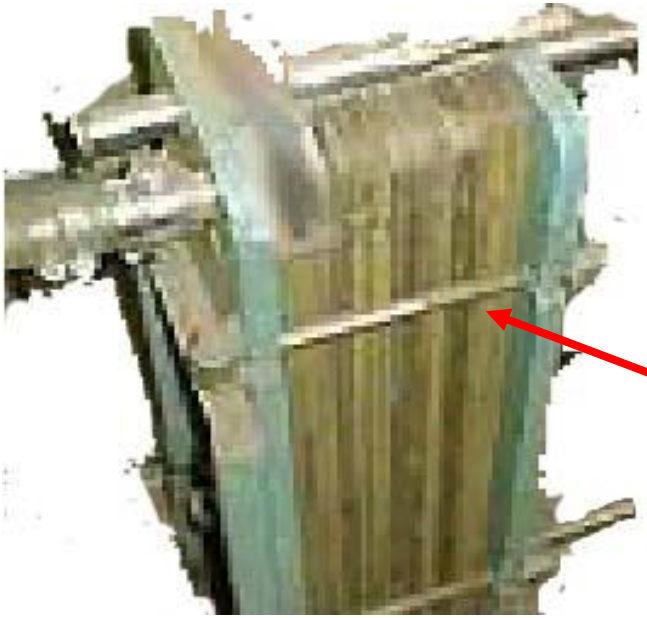
Other checks (3)

Check condition of equipment



Corrosion on plates of heat exchangers indicates possible contamination

Staining on water storage tanks

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Other checks (4)

Maintenance records, maintenance of pump seals and O rings

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Other checks (5)

Air filters

- Integrity testing
- Sterilization and replacement frequency
- Check burst discs

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Other checks (6)

- Temperature-compensated conductivity meters
- Influence of plastic pipe adhesive on TOC
- Non-condensable gases in pure steam

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Other checks (7)

- UV light – monitoring performance and lamp life and intensity
- Validating ozone dosage
- Specifications for acids, alkalis for DI and sodium chloride for water softener
- “Normally open” and “normally closed” valves

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Documentation review may include:

- Qualification protocols and reports
- System review
- Change control request (where applicable)
- Requalification (where applicable)
- QC and microbiology test results and trends, OOS and OOT
- Procedures and records

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Sampling (1)

- Review the sampling procedure (SOP) with a sampling plan (user and sampling points)
  - Sample integrity must be assured
  - Sampler training
  - Sampling point , sample size, sample container and label
  - Sample transport and storage
    - When is the test started?
  - Test method – is the filtration method used? Which media?

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Sampling (2)

- Verify compliance with the procedure and plan
- Ensure that samples were taken and not skipped
- Review trends
  - Alert and action limits, 2 sigma
- OOS, OOL, OOT results
- Investigations and CAPA

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Testing

- Review method verification
- Chemical testing
- Microbiological testing
  - *test method*
  - *types of media used – preferred R2A*
  - *How was the media sterilized – validated procedure*
  - *incubation time and temperature*
  - *objectionable and indicator organisms*
  - *Manufacturer's specifications*

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Suggested bacterial limits *(CFU/mL)*

See Pharmacopoeia

Sampling location	Target	Alert	Action
Raw water	200	300	500
Post multimedia filter	100	300	500
Post softener	100	300	500
Post activated carbon filter	50	300	500
Feed to RO	20	200	500
RO permeate	10	50	100
Points of Use	1	10	100

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Pyrogens and endotoxins

- Where required, verify testing for pyrogens and endotoxins
- “Pyrogen” : When injected into mammals – will give rise to fever
- Endotoxins are pyrogenic, come from Gram negative bacterial cell wall fragments
- Detect endotoxins using a test for *lipo-poly-saccharides (LPS)*
  - *rabbit test detects pyrogens*
  - *LAL test detects endotoxins*
- Ultra-filtration, distillation and RO may remove pyrogens

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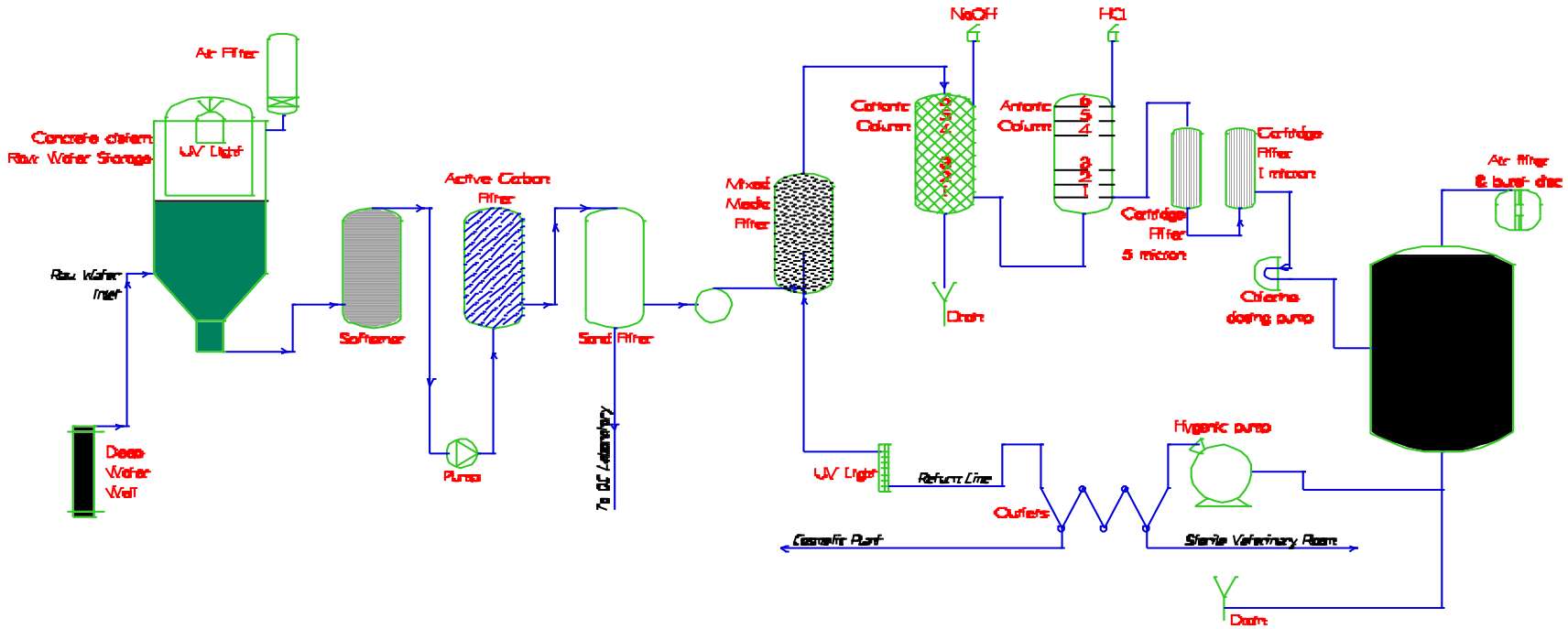
Group Session

- You are given a schematic drawing of a water system to discuss. List any problems you identify and discuss their solutions



INCORRECT WATER TREATMENT PLANT

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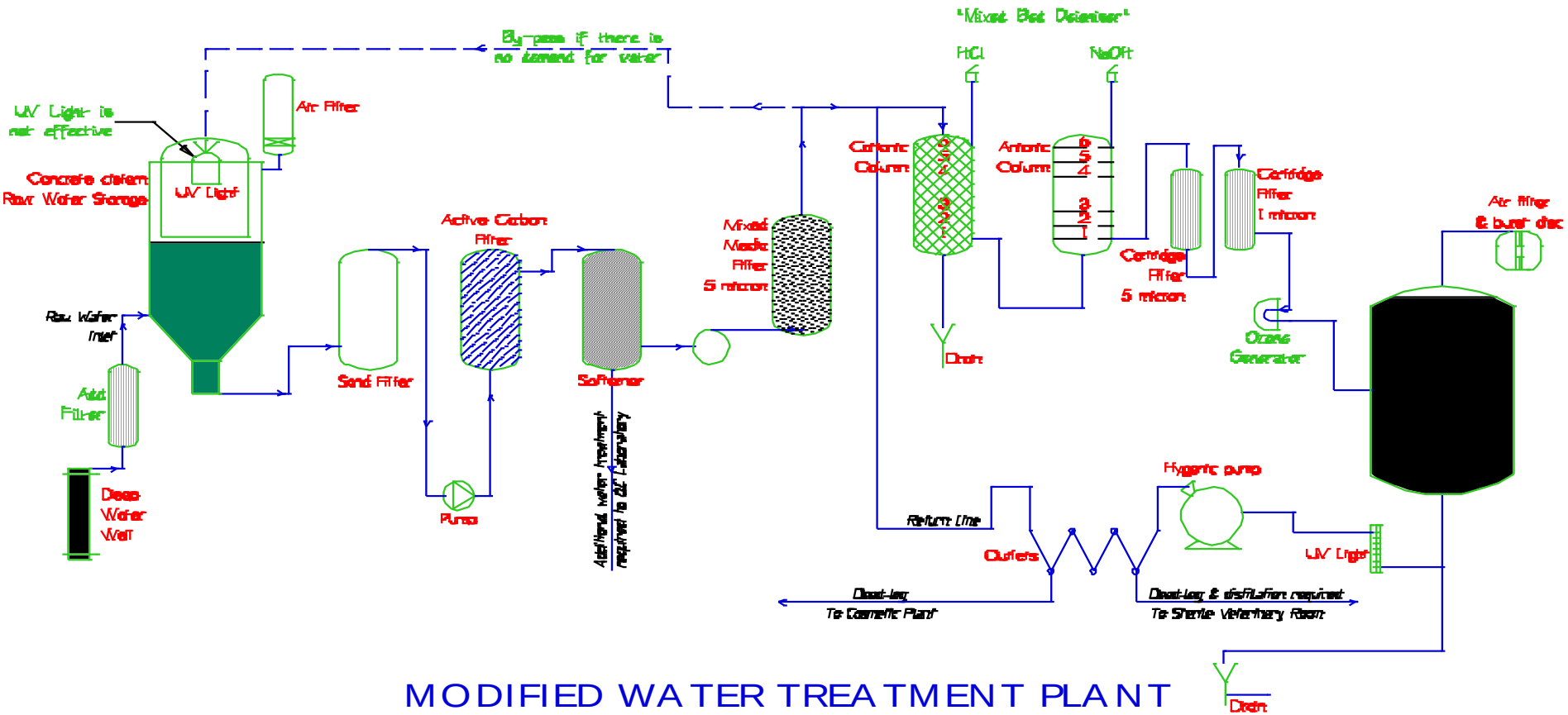
Group Session



MODIFIED WATER TREATMENT PLANT

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