EMA
Production of WFI non-distillation methods
Q&A

Georg Göstl

Baxter AG

September 2016

History

- Q&A document
- Adopted by GMP / GDP IWP May 2016
- Start of public consultation 5 August 2016
- End of consultation (deadline for comments) **4 November 2016**

Intention:

Preliminary guidance until on-going revision of Annex 1 of the GMP guide is complete

Introduction

Ph. Eur WFI monograph (0169) revised to include, in addition to distillation, **reverse osmosis (RO) coupled with suitable techniques**, for production of WFI

Monograph 0169:

- WFI obtained from water that complies with water for human consumption or from purified water
- Produced either by distillation or by purification process equivalent to distillation. RO coupled with other appropriate techniques (**electro-deionisation, ultrafiltraion or nanofiltration**).
- **Notice is given to supervisory authority before implementation** (for 3rd countries: authority of the importer, MRA-countries: authority responsible for GMP oversight in the country concerned)
- Correct operation **monitoring** and **maintenance** are essential
- Validated procedures, in-process monitoring (**conductivity**) and regular monitoring of **TOC and microbial contamination**
- First portion of water (begin to function) is discarded
- WFI in bulk is stored and distributed to prevent growth of micro-organisms and to avoid contamination

Design

Design as to minimise risk of microbiological contamination and proliferation

Control Strategy:

- Take into account **risks in use of RO,** measures to address those risks and various control measures to provide adequate assurance of water quality, or specific measures to enable identification of any issues which may impact water quality
- Additionally, **potential for biofilm formation** assessed and measures put in place to minimise formation of biofilm (see **Section 2**)

Materials of construct:

- Must not be **reactive, additive or absorptive**
- Permit **routine steam sanitisation along with routine chemical sanitisation**
- **Good design practice** to minimise areas of reduced flow

Design

Pre-treatment:

- Adequate **removal of organic particles** and **microbiological impurities** - ozone (its use requires compatible materials of construction)
- **Control of scaling** – ion exchange upstream of the membrane
- **Control of fouling** – depth or media filtration
- Removal of microbial control agents – Chlorine (activated carbon or chemical reducing agents)
- Detection of residual free chlorine with oxidant-reduction potential electrodes
- Other agents (chlorine dioxide, hydrogen peroxide, ozone, permanganate)

Techniques such as deionisation, water softening, descaling, pre filtration, degasification, nanofiltration, electro-deionisation, ozonation, UV treament and micro-filtration should all be considered during design phase

Pre-treatment to ensure **feed water of adequate quality,** thereby protecting the membrane, minimising membrane degradation, and aid minimising risk for microbiological proliferation and biofilm formation

The quality of RO feed water should be **monitored.**

Design

RO membranes:

- Robust enough to permit routine **high temperature sanitisation** along with **routine chemical sanitisation** (development and evolution of membranes: higher temperatures, pressure and more harsh chemical sanitisation must be applied)
- Membranes should be **routinely tested** for any potential integrity breaches
- **Double pass RO membranes** should be considered
- Additional techniques to be considered:
  - Nanofiltration
  - Electro-deionisation
  - Ultrafiltration (known to have an endotoxin reducing capability)
  - Microfiltration/ultrafiltration (remove microorganisms, membranes made from chlorine resistant material)

Design

Total Organic Carbon:

- **On-line TOC meters** must be employed as a prerequisite and **located at various positions**; location **based on risk assessment**:
  - feed water,
  - downstream of pre-treatment,
  - post RO-membrane and UV-lights,
  - post final treatment delivery to storage tank
- Automated diversion through a **recirculation system when quality of water is outside acceptable limits**; resulting in reporting under the PQS (frequency monitored and root cause investigated appropriately)
- When on-line TOC systems fail, robust corrective measure
- **Alert limits** based on **data generated during** system performance throughout **qualification phases** and commensurate with operating capabilities
- Alerts **routinely reassessed** to enable, where possible, **tightening.** Increasing of such limits is **not good practice** and may mask a failing system

Design

Conductivity:

- **On-line conductivity meters** must be utilised as a prerequisite and be installed at various locations (take into account locations of TOC-meters, but also consider monitoring of **RO concentrate and permeate** (determine and trend rejection from system).
- Changes in **rejection percentages** can be indication of membrane failure, seal failure, improper pH, feed pressure issues and increasing scaling or fouling
- **Trend data should be reviewed routinely** (determine potential for deterioration in the system)
- When on-line conductivity systems fail, robust corrective measures

Design

Sanitisation:

- System designed to allow routine sanitisation
- **Frequency based on risk assessment** and on data gathered during qualification
- Monitoring of flora to allow adaptation of sanitisation procedure, based on resistance of concerned microorganisms
- Enable **routine steam sanitisation** (distribution loop and storage tanks).
  RO membranes currently not designed to withstand pressurised steam, but those capable should be utilised
- **Chemical sanitisation:**
  - Peracetic acid
  - Sodium Hypochlorite
  - Hydrogen Peroxide
- Appropriate **contact times** for sanitisation need to be established
- **Ozonation** should be incorporated, resistance of materials against ozone
- It is unlikely that a distribution stem with non-stainless steel components would be acceptable
- **De-ozonation** must be performed. UV irradiation typically used.

Design

Qualification:

- Follow **good engineering practice**
- Performance of the system must be proven over extended period of time
- Sampling programme must be sufficiently robust
- **Initial validation period (testing on all points) should be extended** to build confidence that system is operating as designed
- **Subsequent phases of validation should be robust** and capture significant data to verify ongoing capability of the system

Design

Sampling:

- During initial qualification:
  - Locations to include:
    - Feed / raw water source
    - Stages of pre-treatment
    - Pre and post RO membrane
    - Post final purification phase
    - Storage tank
    - All user points
    - Return loop post final user point
  - Typically sampled and tested daily for a specified period of time
- Next phase:
  - Take account of above locations
  - Frequency in a manner to assure satisfactory performance over extended period (Typically over a year to take account of e.g. seasonal variations)
- Routine operation:
  - Daily sampling
    - All user points utilised on the day
    - Return loop
    - Points both pre and post RO membranes
- Volumes sampled for microbiological monitoring justified and commensurate to test requirements

Design

Tests:

- In line with Ph. Eur. Monograph 169
- Use of **rapid microbiological methods** as a prerequisite
- **Rapid Endotoxin testing**
- Quantitative microbiological methods
- Due consideration to employing **alternative methods for rapid quantitative determination of contamination**. Validation of such systems in line with Ph. Eur. 5.1.6 ‚Alternative Methods for control of Microbiological Quality'
- **Alternative / rapid methods should be employed**
- Alert limits based on statistical data analysis
- **Trend data** reviewed routinely, **adverse trend** appropriately investigated
- Review of trend data **not only % alert and % actions, but also review raw data** (e.g. identifications)
- Alerts reassessed routinely to enable tightening of limits; increasing such limits is not good practice

Design

Preventive Maintenance:

- Routine regeneration of pre-treatment systems
- Replenishment of resin beds (as required)
- Change out of filters, gaskets, seals and RO membranes
  - Defined frequency or
  - Following adverse indicators, as well as
  - Routine sanitisation
- Detailed inspection checks incorporated into such routine PM to take account of potential for formation of a biofilm
  - Inspection for leaks
  - Inspection of condition of gaskets and seals
- Performance of RO membranes assessed during routine PM including determination that pressures and flow rates are in line with satisfactory operation of the system

Biofilm

Measures should be taken to put in place **scientifically justified mechanisms for maintaining biofilm control,** and prevent further formation of such biofilms following proven methods for cleaning and sanitisation

Approach to maintain control:

- **Control strategy** developed
  (assess risks and determine acceptability of control measures)

- Effectiveness of **sampling and testing regimes** critically assessed
  in conjunction with development of a control strategy

Biofilm

Control strategy:

- Take account of **design of process (ultimately prevent or minimise risk of contamination**); requires thorough **process knowledge and understanding**
  - Design – plant, process (avoid dead legs, allow full drainage, minimise roughness)
  - Control – in-process controls
  - Monitoring system
  - Prevention – Investigations / CAPA / root cause determination (robust investigation tools)
  - Raw materials
  - Preventive Maintenance – to not add significant risk for contamination
  - Equipment and facilities
  - Process qualification
  - Personnel
  - Utilities
  - Cleaning / sanitisation
- **Contamination control**: series of successive linked events/measures; typically assessed and monitored in isolation. **QRM tools** along with **scientific judgement** to determine **critical control points**. Integrate all those measures for more comprehensive approach
- **Iterative process taking into account all information throughout lifecycle**

Biofilm

Steps to eradicate or remove existing biofilms:

- Both **chemical and physical removal** (hot water flush known not to have a significant effect) to both **penetrate and kill the organisms** in question
- Ensure that system is in **recirculation mode**
- Any **approach to biofilm removal** needs to an active in operational strategy
- Appropriate **removal of cell debris**
- Rotation of **disinfectants & detergents** and inclusion of **sporicial agents**
- Any biofilm removal should be followed by intense monitoring before returning the system to use
- A **robust PM programme is essential** (regular inspection of utilities, equipment and transfer lines – O-rings, gaskets, seals – regular inspection and replacement)
- **Specific agents (appropriate contact times** need to be established):
  - Sodium Hypochlorite
  - Hydrogen Perxide / Peracetic acid solutions
  - Ozonation (water system)
  - High temperature or steam sanitisation
- **Singular approach not acceptable**; a minimum of double-edged approach (e.g. **high-temperature in conjunction with chemical sanitisation** at a set frequency based on risk assessment)

Biofilm

Additional measures to increase probability of detecting biofilm:

- **Robust sampling plan** (each potential source of contamination incorporated)
- **Effectiveness of EM programme** formally assessed at minimum annually
- **User points** should be **tested each day of use**
- **Routine identification of contaminants is critical** (any shift in the flora)
- Use of **more sensitive endotoxin detection methods**
- **Alert limits** based on capability of the system; any change or trends appropriately investigated
- **Frequency of trend analysis and use of trend data is critical**
- Use of **rapid microbiological test methods** and systems should employed (improve early detection and allow timely action)