New World for WFI Systems Starting in 2017 ?

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USP Chemical Analysis Expert Committee

[Responsible for Pharmaceutical Water]
2010-2015 (USP 34-38) and 2015-2020 (USP 39-43)

USP Pharmaceutical Water Expert Committee
2000-2005 (USP 24-28) and 2005-2010 (USP 29-33)

PhRMA Water Quality Committee
(USP Advisory Council for USP 23 Water Changes)

USP Disclaimer

I am an unpaid volunteer working with USP.

I am not speaking for or representing USP.

I am speaking as a private citizen.

Opinions expressed are my own, not USP's.

My intent is to benefit the public health (same as USP's).

Presentation Summary

- Why a “New WFI World”
- Challenge of tight microbial and endotoxin control
- History of WFI microbial specifications
- Microbial Control = Endotoxin Control (mostly)
- Forms of Endotoxin and removal strategies
- Sounds easy. How hard can this be?
- Cost impact of EP WFI monograph changes
- Anticipated problems
- Validation and inspection scrutiny
- Avoiding easily preventable excursions
- Who wants to be first?

Why a "New WFI World"

- European Pharmacopoeia (EP) finally changing WFI monograph for Production of WFI (eff. 4/2017)
  - Formerly Distillation ONLY
    - Impact: Europe a big market, so even though USP and JP allowed non-distillation approaches, everyone forced to use expensive distillation to sell into this market
  - As of 4/2017, it will be Distillation or RO-plus
    - It is produced either by distillation …or by reverse osmosis, which may be single-pass or double-pass, coupled with other suitable techniques such as deionisation and/or ultrafiltration.
- Impact of this major change
  - WFI can be made more cheaply without heat – but tricky
    - Heat/hot water definitively effective against biofilm
    - Biofilm and Endotoxin harder to control without heat
  - Companies w/o experience now going to make WFI !

Why Is Microbial and Endotoxin Control an Important Challenge?

- WFI expectations very tight for microbial count and endotoxin
- Microbiome of water systems mainly Gram negative pseudomonads as biofilms
- Water system biofilms release bacteria that contain endotoxin
- WFI distribution systems must prevent biofilm
- WFI generation systems must minimize biofilm and prevent passage of incoming endotoxin
- WFI generation and distribution systems probably at an ideal biofilm growing temperature

History of WFI Microbial Limits(1)

- FDA not silent on WFI microbial limits
  - 21CFR 212 “LVP CGMPs” (1976) -- micro limit of “not more than 10 microorganisms/100mL
    - Law never passed but limit used by early adopters
  - FDA Guide to Inspections of High Purity Water Systems (1993) -- 10 cfu/100mL as Action Limit
- Prior to 1985 no micro limits in USP for WFI!
- In 1985 (USP XXI), <1231> stated WFI micro limit of 50 cfu/mL (not in monograph, so not mandatory)
- From 1990-1996 (USP XXII – USP 23) <1231> silent on WFI micro limits (also not in monograph)

History of WFI Microbial Limits(2)

- USP 23 – S5 (1996) <1231> rewritten to include a 10cfu/100mL Action Level
- USP 28 – S2 (2005) <1231> again rewritten to mention a user-established Specification and a trend-based Action Level maximum of 10cfu/100mL
- USP 39 – S2 (2016) <1231> rewritten yet again to mention trend-based Alert and Action Levels and a user-established Specification not greater than 10cfu/100mL
  - In <1231> (advisory, non-mandatory), not in monograph
  - Change intended to express 10cfu/100mL as the Specification FDA considers it to be and end confusing misuse of “Action Level” term as a Specification synonym

Microbial Control = Endotoxin Control (mostly)

- Since the endotoxin comes from Gram negative bacteria in the system, controlling the bacteria will control the endotoxin as well, right?
  - Yes, for endotoxin originating in the distribution system
  - Yes, for endotoxin originating in the purification system
  - NO, for endotoxin in the source water
- Fortunately, endotoxin is relatively easy to remove from the source water because of its forms and properties (size and charge)
- First remove endotoxin from the source water, then keep biofilm from growing and adding it back

Forms of Endotoxin

- Whole Gram negative cells (live or dead)
  - Micro-filtration and smaller, even MM filters
- Cell wall fragments of dead G- cells
  - Small pore sub-micron filters and smaller probably remove most (< 0.02 µm rating)
- Free-endotoxin
  - In water, does not exist as free monomers (average monomer size of ~20,000 Daltons, with range of ~10,000 – 25,000 Daltons)
    - Amphipathic nature (hydrophilic and hydrophobic ends) makes it form vesicles or micelles with other monomers
    - Hydrophilic ends on outside, hydrophobic ends on inside
  - Micelles of 5 – 50+ monomers = 50,000 – 1,000,000+ Daltons
  - Easily removed by RO, NF and UF because of size
  - Since hydrophilic end is negatively charged, removed by DI/EDI

How Hard Can This Be?

- Sounds easy: Get it clean, then keep it clean
  - The difficulty is not getting the water clean
  - The difficulty is keeping the water clean
- Biofilm can be persistent and hard-to-kill
  - Heat is very effective, chemicals are not (crevices!)
- Evolved practice is to use distillation (heat) to purify, then heat to maintain purity - very “forgiving”!
  - Bacteria definitively killed and can’t grow at high temps

D-values at 60°C, 65°C, 70°C, 75°C, & 80°C are about 49sec*, 5sec*, 0.5sec**, 0.05sec**, & 0.005sec**

*Spinks, A.T., et al. (2006) Thermal inactivation of water-borne pathogenic and indicator bacteria at sub-boiling temperatures. Water Research 40:1326–1332

**Estimated from z-value of 5°C (10-fold change in D-value for every 5°C change)

Martinez, J.E., Hyperthermophilic Microorganisms and USP Hot Water Systems, Pharmaceutical Technology, Feb 2004, pp 50-65.

  - But heat, stills, and heated systems very expensive
  - Hot WFI system problems usually in cool sub-loops
  - Cool systems where biofilm could grow = problems!

Impact of EP WFI Changes

- Door opened for closer compendial harmonization
- Door opened for cheaper non-distillation technologies to make WFI
- When heat not used to purify by distillation, heat may or may not be used to maintain purity
  - Biggest operating cost savings avoids routine use of heat
  - Why use costly heat for loops if not already leveraged from purification (hot distillate)
  - Biggest capital cost savings avoids heat (e.g. plant steam boilers, stills, heat exchangers, pipe and tank insulation, heat tolerant MOCs)
    - True if using chemical sanitizers
    - Not true if using Ozone (~= to heated system cost)
    - Not true if heat is a back-up sanitization option
- But remember, Cool systems = problems!

What kinds of problems?

- Cool systems can allow biofilm development
  - Ozonated systems usually not problematic, but expensive
  - Cheaper chemically sanitized systems often problematic unless:
    - Well-designed with good MOCs, welds, minimal crevices (expensive)
    - Monitored frequently (expensive)
    - Have ongoing system controls like UV or ultrapure water (expensive)
    - Sanitized frequently (impractical and expensive)
- When cost is the primary driver for a budget-challenged firm, GMPs, expertise and training often also deficient
  - Heat is “forgiving” of poorer micro/endo control expertise
  - Maintaining micro/endo control in non-hot systems requires MORE
    - Process understanding
    - Experience and training
    - Attention to detail
  - Cost of WFI was “only” impediment into parenteral manufacturing
    - Some firms should just NOT make parenterals – lack of expertise

Validation Expectations

- Qualification of a non-distillation, cool WFI system will receive detailed regulatory attention
  - Not the traditional unproblematic hot WFI system
  - Unforgiving - Not as easy to control micro/endotoxin
  - Very tight specifications for a cool system
    - Expect more protocol/data deviations due to sampling issues
  - Greatest patient risk from a post-validation bad system
  - Regulators (inspectorate and application reviewers) need more convincing to neutralize paradigms
- Validation expectations may be more stringent
  - Focus on URS and DQ (usually easy for hot systems)?
  - Longer phase durations, ↑ sampling frequencies?
  - Special attributes (toxins: known ,unknown, unlikely)?

Site Inspection Issues

- Basically have no idea what to expect
- Cold WFI system design and operation likely to be challenged, if not “belts and suspenders”
  - European inspectorate likely to be pickier
  - Already have paradigm of impossibility
  - Suspected data fraud - “Guilty until proven innocent”
- Water system monitoring deviation investigations will probably be an inspection focus
  - Should not be many (like hot WFI systems)
  - If there are any (likely with cold systems), all but most recent ones closed, CAPAs completed
  - Be sure sampling and water use procedures are appropriate and consistently executed – min. excursions

Avoid Common Excursion Causes

- System excursions reveal system adequacy
- Investigation and resolution of excursions and their root causes reveals system expertise
- Number and resolution of excursions is always an inspectional focus and gauge of user competency
- Avoid misrepresenting system as being inadequate by having easily avoidable excursions
- Avoid common excursions by proactively correcting excursion root causes before they happen
  - Chemical Excursions
  - Microbial Excursions
  - Endotoxin Excursion

Avoid Common Excursion Causes

- Common chemical excursion avoidances
  - Avoid TOC excursions
    - Use semiconductor/nuclear grade DI resins
    - Collect off-line TOC samples ONLY with certified low TOC containers (<5 ppb)
  - Avoid Conductivity excursions in ozonated loops
    - Dump part of system water after a non-working periods greater that 1-2 days
    - Establish distribution system bleed during non-working periods
  - Avoid Conductivity excursions in RO systems
    - Assure complete chlorine removal that could damage RO membranes
    - Avoid over-concentrating impurities by having no more that 70% recovery
    - Reduce RO membrane fouling by good pretreatment softening and membrane cleaning (scale and biofouling) at a proper frequency, avoiding over pressurizing to compensate for fouling and reducing purity
    - Use anti-scalants in RO feedwater to reduce membrane fouling
    - Use temp and pH adjustment to RO feedwater to improve RO performance
    - Use hot water sanitizable RO/EDI systems to keep clean & improve performance
    - Monitor conductivity of RO/EDI output on-line, use divert valve plumbing if bad

Avoid Common Excursion Causes

- Common microbial excursion avoidances
  - Use weekly hot distribution sanitization if not continuously hot distribution (80°C). If 65°C used, flush outlets with the hot water.
  - If heat-sanitizable distribution is not used, use continuous ozone in the tank and weekly or more frequent loop ozonations
    - Assure downstream sides of outlets are ozonated by flushing or capping and leaving valve open during loop ozonation
  - If chemical sanitization is used (doable, not wise), use stringent and thorough treatment (e.g. 1% Minncare, many hours, ALL surfaces, at least monthly) less frequent with UV in loop and incoming tank water
    - Design in back-up sanitization approach, e.g. heat , ozone, other chem
  - Use hot water sanitizable RO/EDI to avoid biofilm development on the permeate side of the membrane
  - Sample in an absolutely consistent (and correct) fashion with ample flushed water collection (fully open valve for ≥30s, or ≥8ft/s for ≥30s)
  - Control manufacturing hose maintenance, storage, handling, & use
    - Best practice – Fresh resterilized hose/gasket every use or at least every day
    - Next best practice – Fresh resterilized hose/gasket every week, stored as ∩

Avoid Common Excursion Causes

- Common endotoxin excursion avoidances
  - Same as Microbial excursion avoidances
  - Same as Conductivity excursion avoidances for RO system
  - If sanitizing after a long period of use (> 2 weeks), flush out all or most of system water and replace with fresh
    - Flushes out endotoxin released from any killed biofilm
  - Routinely monitor endotoxin levels in source water with a quantitative assay (appropriate sample dilution and std curve range)
    - Whenever high level periods are detected or predicted from historic monitoring, increase system monitoring frequency to detect possible breakthrough early
  - Adequately control the biofouling of the carbon bed (if used) by daily to weekly hot water sanitization, backwashing, etc.
    - After hot water treatment, flush several bed volumes to drain to remove released endotoxin from killed biofilm and avoid over-burdening the RO system with high endotoxin levels
  - Monitor endotoxin levels in distribution system with a sensitive quantitative assay, e.g. Endosafe® with most sensitive std curve
    - Track trends against upstream testing. maintenance, and other events

Who wants to be the first guinea pig?

- We know roughly what it will take to make and keep WFI quality with a cold system – many potential gains
- We can guess, but no one really knows how stringent the regulators will be at first or later on
- If this is your first venture into the world of WFI, wait until someone else does a cold WFI system – learn the validation and inspection pitfalls vicariously
  - Especially after a European inspection
- If you are very familiar with traditional WFI systems and are simply turning to cold WFI for operational and economic reasons,

GO FOR IT!

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Thanks for your attention!

THE END