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

▲ 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!
Presentation Recap

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Thanks for your attention!

THE END