Webinar 2019

WFI using non-distillation Methods –
the ISPE D/A/CH Approach

ISPE D/A/CH
COP Pharma Water & Steam

Fritz Röder
Merck KGaA, Darmstadt,
Germany

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Speaker

Fritz Röder

Senior QA Manager
Merck KGaA, Darmstadt, Germany



Fritz is a recognized expert in the pharmaceutical industry. He has large experience in pharmaceutical media supply, GMP environments and the processing of solid, semisolid and liquid (sterile) dosage forms.

Member of:

- EDQM Working Group "Water"
- ISPE DACH Expert Group "Water & Steam"
- PDA

Experience:

- Managed various large projects involving solid, semi-solid, liquid sterile dosage forms
- Contributed to several audit projects (FDA, ANVISA, German RP, Russia ,…)
- GMP consulting in various technical questions
- Water treatment & TOC measurement design
- Responsible operator of GMP equipment
- Currently Senior Manager Validation, Qualification & Engineering at Merck KGaA, Darmstadt

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Content

- The Regulatory Overview of WFI
  - History
  - Current Situation ➔ EMA Q&A on WFI
- The new ISPE D/A/CH Handbook
  - What are the risks if membrane technology is used?
  - Differences between HPW and WFI
  - The Final Treatment Step
  - Storage, Distribution, Sanitization
  - Qualification, Monitoring, Cost Comparison
- Help, HPW has been deleted from the Ph. Eur.! What can I do?

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Regulatory Overview – History

From the USP I (December 21, year 1820):

- „Aqua distilleteur vasis permundis, donec ejus duo circiter trientes stillaverint. Aquam distillatum in lagena vitrea servato.“

Translation:

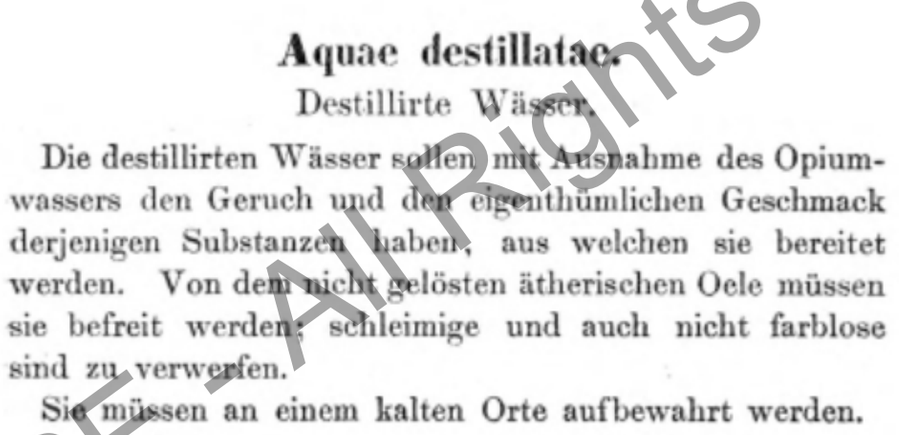
- “Let water be distilled in clean containers until about two thirds have come over. Store the distilled water in a glass bottle.”

➔ The only substance in the pharmacopoeias where the process technology has been described

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Regulatory Overview – History

From the first Pharmacopoea Germanica (year 1872):



Aquae destillatae.

Destillirte Wässer.

Die destillirten Wässer sollen mit Ausnahme des Opiumwassers den Geruch und den eigenthümlichen Geschmack derjenigen Substanzen haben, aus welchen sie bereitet werden. Von dem nicht gelösten ätherischen Oele müssen sie befreit werden; schleimige und auch nicht farblose sind zu verwerfen.

Sie müssen an einem kalten Orte aufbewahrt werden.

Translation: "Distilled waters (except opium water) shall have the odor and the taste of the substance they have been made of. Non-dissolved oils must be separated from the water; slimy or colored water must be discarded. Store the water cold."

➔ Ph. Eur. started in 1964

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Regulatory Overview – Current Situation

There are many regulations worldwide containing anything about Water for Injection

- ISPE Baseline® Guide: Water & Steam Systems (Link)
  - ISPE Good Practice Guide: Ozone Sanitization of Pharmaceutical Water Systems (Link)
  - ISPE Good Practice Guide: Sampling for Pharmaceutical Water, Steam, & Process Gases (Link)
  - **New: ISPE D/A/CH Handbook WFI using non-distillative Methods** (Link)
- EU-GMP-Guide (Link)
  - Annex 1, Annex 15
- VDI 2083 Blatt 13.1 and 13.3 (german)
- FDA Guide to inspections on High Purity Water systems (Link)
- USP Monograph Water for Injection
- USP chapter <61>, <62>, <85>, <643> <645>, <1231>
- Ph. Eur. Monographs 0169 (WFI), 1927 (HPW, deleted)
- Ph. Eur. chapter 2.2.38, 2.2.44, 2.6.12, 2.6.13, 2.6.14, 5.25 (draft)
- EMA Note on Guidance on Quality of Water for pharmaceutical use (Link) (Link new draft)
- EMA Q&A on production of water for injections by non-distillation methods (Link)
- WHO TRS 929, Annex 3 (Link)

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Regulatory Overview – Current Situation

Since 04/2017, the European monograph 0169 allows to produce WFI:

- 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; or
- by a purification process that is equivalent to distillation. Reverse osmosis, which may be single-pass or double-pass, coupled with other appropriate techniques such as electro-deionisation, ultrafiltration or nanofiltration, is suitable. Notice is given to the supervisory authority of the manufacturer before implementation.

For all methods of production, 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 monitoring of total organic carbon and microbial contamination are applied.

The first portion of water obtained when the system begins to function is discarded.

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Regulatory Overview

- In addition to the new WFI monograph,
  - EMA has issued a new Q&A document on membrane-based WFI
  - The new Annex 1 draft has been published in 12/2017
  - The European monograph for Highly Purified Water (1927) has been deleted in 04/2019
  - A new Note for Guidance has been published in draft (Link)

➔ Especially EMA Q&A & Annex 1 provide room for questions & interpretations

- Who could answer those questions?
  - **The ISPE D/A/CH Handbook!**

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The Handbook in German Language

- Thanks to all authors and contributors
- English version is in progress
- Link



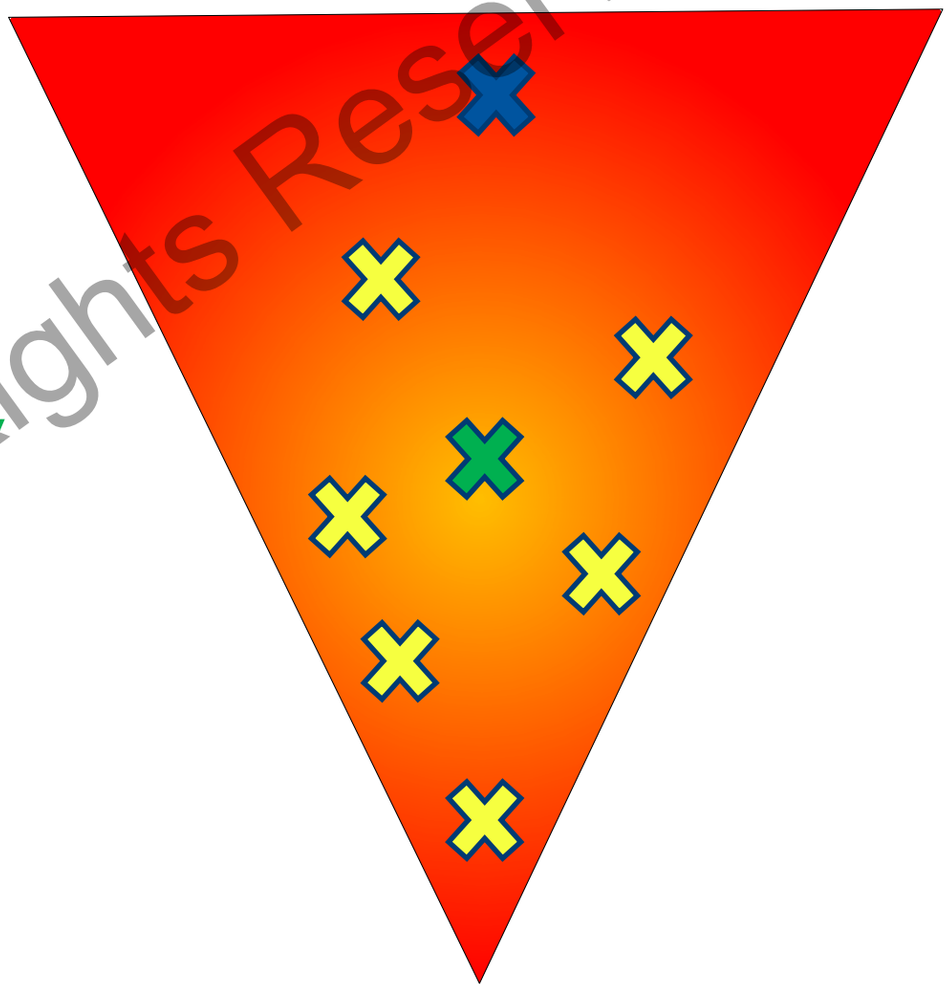
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How much do we have to increase control when operating cold WFI systems?

EMA Q&A: A lot. We have no experience!

ISPE D/A/CH: A bit. Do what is technically advisable, and write it down.

Equipment manufacturers & Pharma companies: depends on the company.
From „not at all“ to „quite much“



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The Risk that changes is the Application Risk

Description	Medicine manufactured using HPW	Medicine manufactured using WFI
Application of the water in medicine used for	Nose Ear Eye Topical preparations	Infusion Injection

The new ISPE Handbook analyses all possible impurities and compares them

➔ Risk consideration

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Content of the new Handbook

1. Forward, Introduction
2. Regulatory Requirements
3. Production of Water for Injection
4. Discussion of Risks
5. Measurement Technology
6. Storage and Distribution
7. Sanitization
8. Qualification and Validation
9. Monitoring and Controls
10. Economic Aspects
11. Conclusion and Outlook

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Control Strategy of RO – a comparison between ISPE and EMA - examples

EMA Q&A recommendations on the control strategy of Reverse Osmosis (RO)	ISPE D/A/CH recommendations on the control strategy of Reverse Osmosis (RO)
Consideration of microbiology, endotoxins, exotoxins	Consider microbiology Assess endotoxins in scope of Ultrafiltration RA Exotoxins: see risk discussion, no frequent testing necessary in routine; typical exotoxin releasing bacteria do not survive in WFI
"routine high temperature sanitization [of RO] along with routine chemical sanitization"	Hot sanitization of a RO system is state of the art Other methods may be advisable if biofilm formation seems to begin
Two-pass RO „to be considered"	single-pass RO + EDI is normally sufficient as well. Decision should be up to the pharma manufacturer
Periodic integrity testing of RO	Possible, but not always necessary in routine
Monitoring of permeate conductivity & differential pressure	Further performance parameters can be calculated using existing process measurement - Flux rate - Salt rejection rate This brings additional process control and process safety

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The Final Treatment Step

The EMA Q&A considers the following technologies for the final treatment step:

- Electrodeionisation (EDI)
- Nanofiltration (NF)
- Ultrafiltration (UF)

ISPE D/A/CH takes the view that **only UF is suitable**:

- Nanofiltration provides only a relative removal (similar to RO) no real barrier ➔ how to validate?
- EDI has no barrier at all
- Ultrafiltration has a barrier. But suitable data is required vor validation

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Ultrafiltration: new aspects in the Handbook

- How can an ultrafiltration be validated for WFI?
  - The first world-wide test standard for cut-off determination has been published!
  - Service life & shelf life
  - Integrity testing
  - Challenge testing
  - Conformity of materials

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UF: Determination of the Cut-Off

Brand new: the first time standard test conditions for cut-off determination have been officially published!

To be considered:

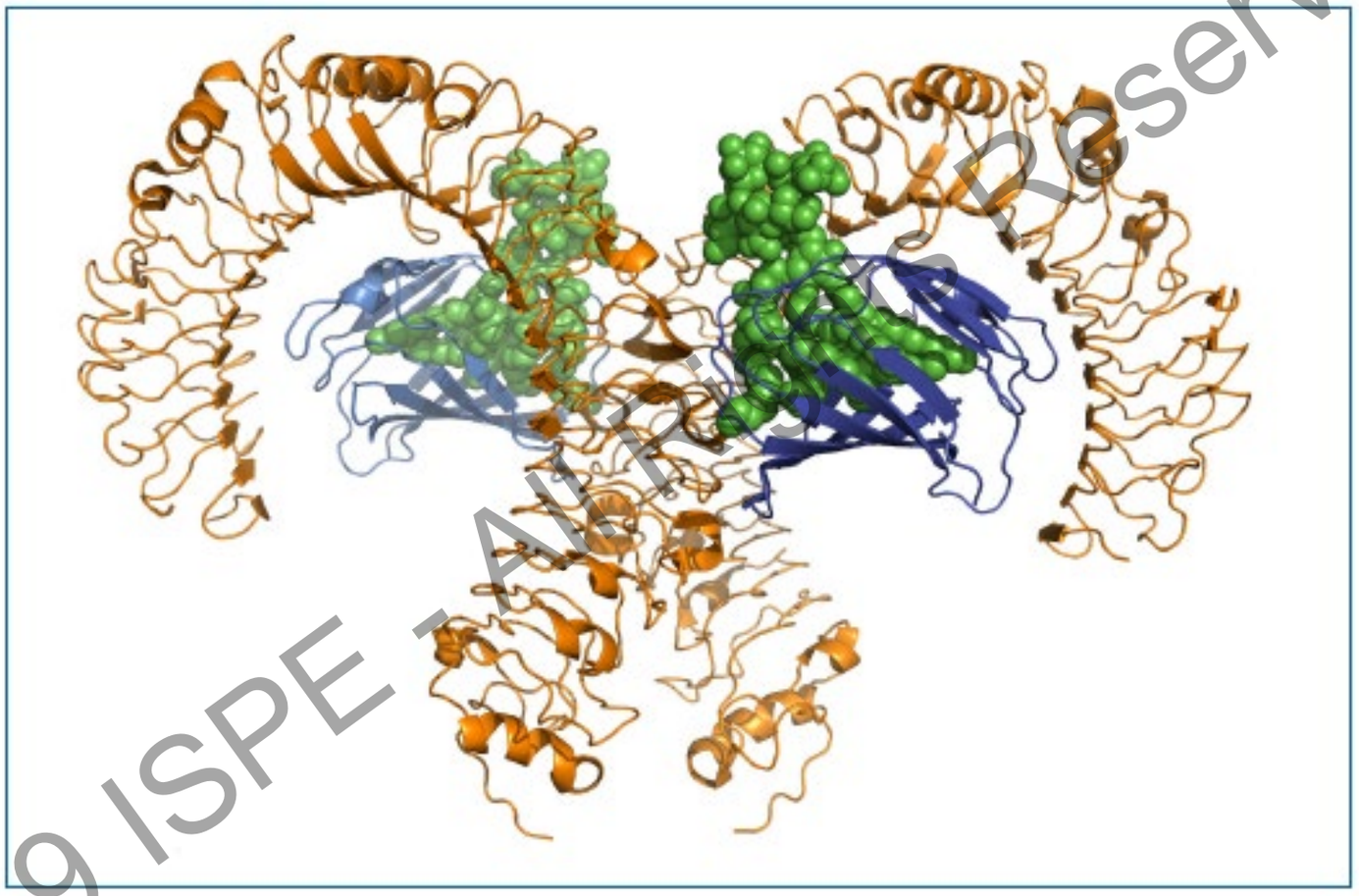
- The right test substance and the right solvent
- The needed retention rate of the substance
- Transmembrane pressure
- Temperature

Which test substances do exist?

- Dextran is a filamentous molecule
- Globule molecules (e.g. insuline) result in better (lower) cut-offs of the UF module
  - ➔ Which form or shape does an endotoxin have?

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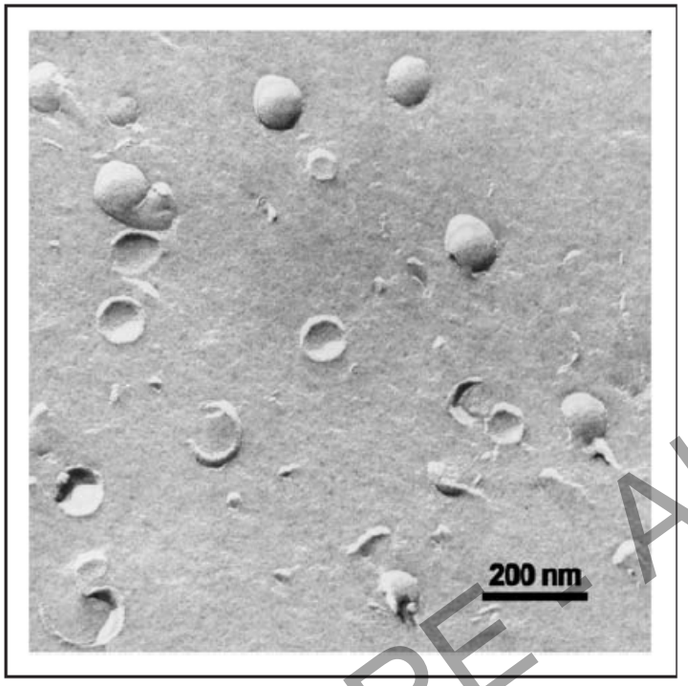
Forms of lipopolysaccharides

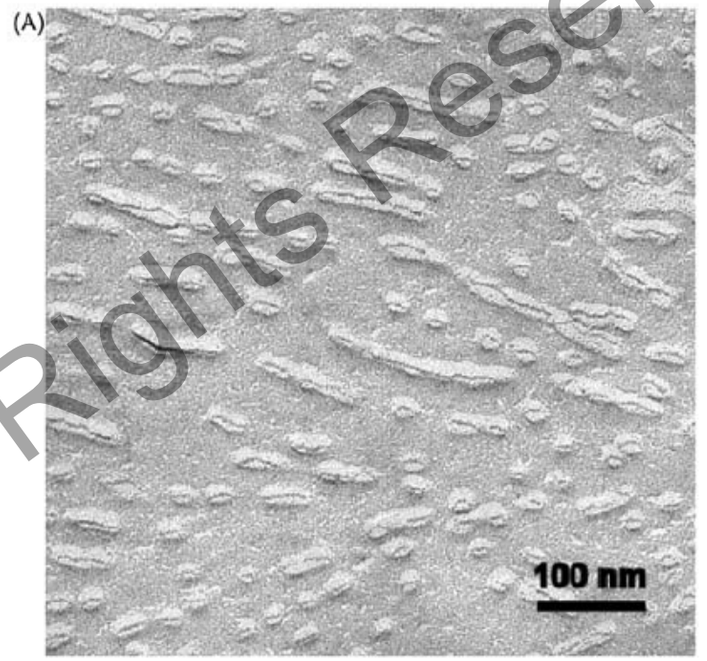


Source: PDA TR 82 (new!): Structural basis of a lipopolysaccharide
➔ no definitive answer can be given

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Forms of lipopolysaccharides – looking through the microscope





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➔ no definitive answer can be given
➔ form depends on different factors (lab method, condition of LPS,…)

Source: http://ini.sagepub.com/content/17/5/427

Test substance: why did we choose Dextran?

- Good sensitivity
- Standard in the Biotech Industry
- Good handling possible

Problem: if Dextran is used for cut-off determination 6.000 Da can practically not be reached

The Japanese Pharmacopoeia specifies a cut-off of 6.000 Da (page 1774)

Endotoxins typically have molecular weights of >20.000 Da (e.g. see german VDI 2083 13.1)

A higher cut-off than 6.000 Da (e.g. 10.000 Da) is considered still sufficient to properly remove endotoxins (e.g. 3-log) if the test conditions are known

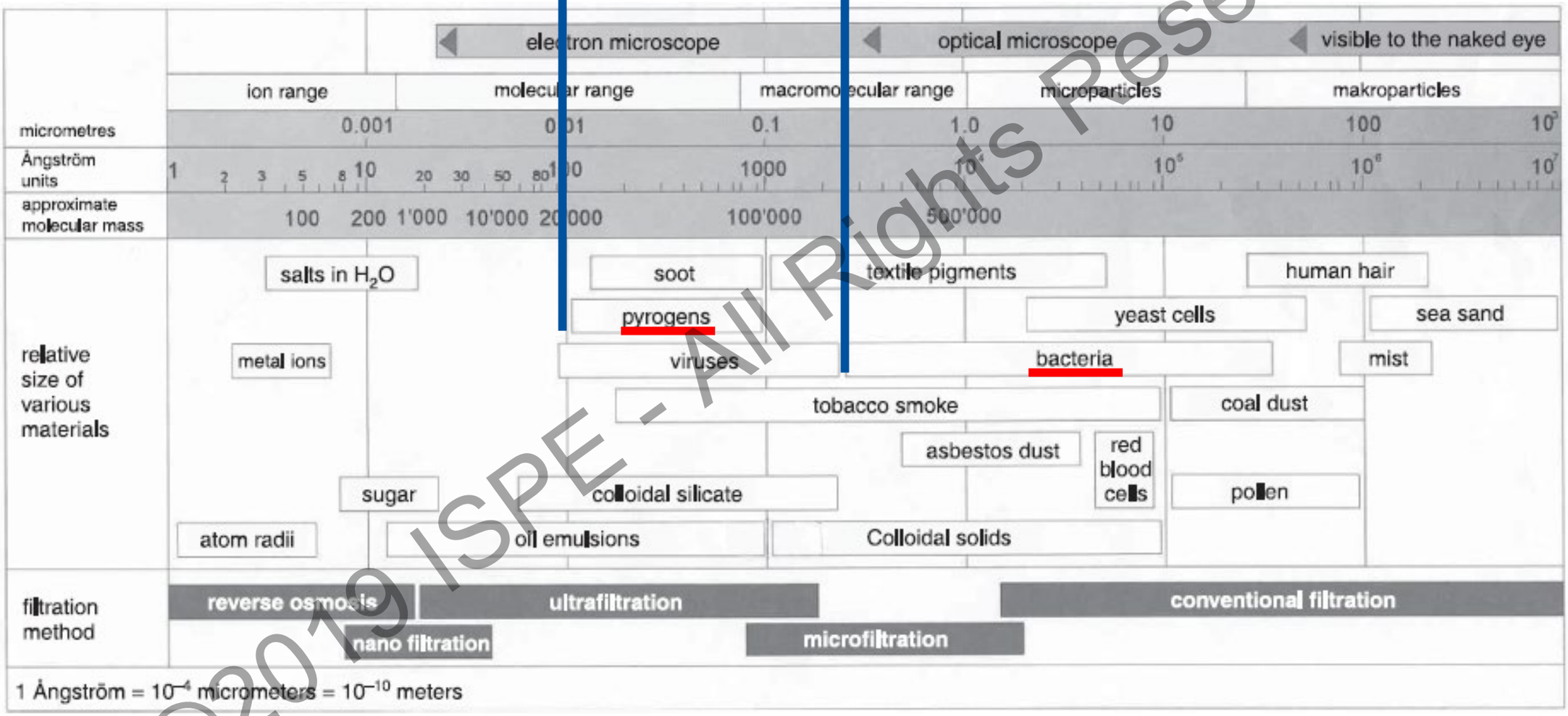
The UF module does not change, only the test method may do!

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Particle sizes of substances and their corresponding separation technology

Min. size pyrogens ➔ UF

Min. size bacteria ➔ sterile filtration



Source: German VDI 2083 13.1 Standard (Link)

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Ultrafiltration: integrity testing

- Possible approaches
  - Bubble-Point Test
  - Pin-Hole-Test
  - Pressure hold test
- If using hollow fiber modules, bubble point testing might possibly harm the module
- According Fick‘s Law the Pin Hole Test can be used here instead of the bubble point
- Ceramic modules are more durable (and expensive), Bubble-Point-Test is less likely to damages

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Conformity of materials (1)

Type of conformity test	Typically used for	Animal testing	Typically applied for WFI
US 21 CFR 170-189.xx	Food	No	Yes
USP <1663/1664> L&E	Injectables	No	No 
USP <88> in vitro testing	Materials staying shortly inside the patient	Yes	Yes
ISO 10993 biocompatibility	Materials staying long inside the patient	Yes	No

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Conformity of materials – the Handbook proposes a change

- Consider replacing USP <88> class VI testing by L&E testing. Why?
  - **Respect** to the animals
- Justification?
  - WFI is not sterile, 10 CFU/100ml
  - No citations known were any patient has been harmed due to WFI quality
  - Product contact? Sterile filtration afterwards
- How does L&E testing work for WFI systems?
  - Only the Extractable test can be performed

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Storage, distribution, sanitization

- Most (not all) considerations that apply to storage & distribution stay similar compared to distilled WFI
- In case of cold WFI generation, cold storage & distribution will be likely as well ➔ ISPE Baseline® Guide: Water & Steam (Link)
- Some cold WFI systems had already been in place before (e.g. if operated with vapor compression)
- Design your tank and loop as small as possible!
- Sanitization:
  - For generation unit: Heat in routine, Chemicals in case of problems
  - Loop: Ozone sanitization is working properly
  - When can you be sure that no more ozone is present in WFI?

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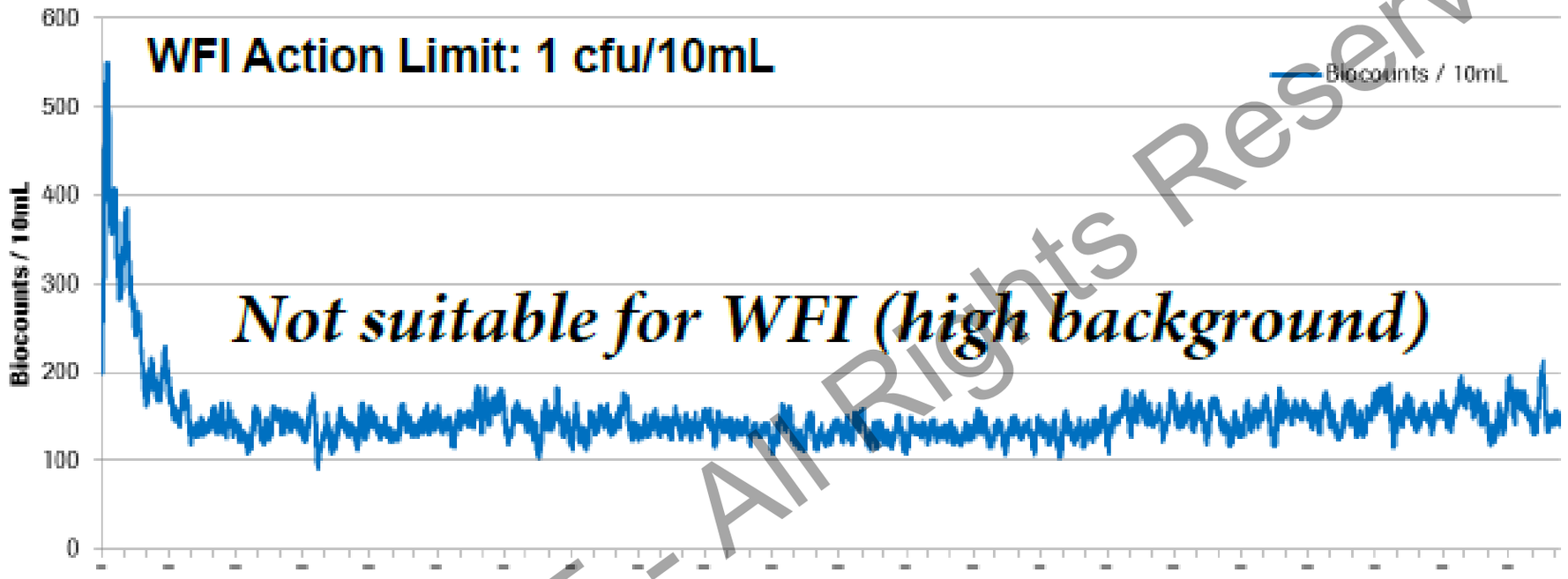
Measurement technology (1)

- EMA Q&A fosters rapid microbiological methods. So far, so good.
- Locations to be considered for TOC / Online AFU measurement
  - Feed
  - After relevant treatment steps
  - Pre / Post RO
  - Before / After final treatment step
  - Tank (flow)
  - All points of use
  - Loop return

  ➔ Nobody can afford measuring all these locations!

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Results from a study carried out at Roche (Azbil IMD-W)



Online-bioburden measurement of WFI:
the noise is higher than the spec (10 CFU/100ml)

➔ AFU and CFU are not comparable!

➔ method validation not yet possible!

Source: Ulrich Georg Zuber, Mike Russ, Peter Kreutzenbeck, Roche/Genentech: Online Water Bioburden Analysis – Expo Lounges 2019, Karlsruhe

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How can we use online bioburden measurement now?

- What does ISPE D/A/CH think on this?
- Online process control is way better than offline sampling
  - But one online bioburden measuring system can measure one location (not more, risk of impurity carry-over)
  - Online bioburden measurement can not be compared to traditional incubation
  - Bioburden measurement may not be used for quality control because the monograph requires incubation

    ➔ Currently only suitable for process control

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Sampling & Monitoring

- Nearly no differences between HPW and hot or cold WFI
  - Sample volume and method remain the same
- From the EMA Q&A:
  - „Daily sampling of the system should be employed for all user points utilised on the day, the return loop as well as consideration of inclusion of points both pre and post the RO membranes."
- From the new Annex 1 Draft:
  - „A sample from the worst case sample point, e.g. the end of the distribution loop return, should be included each time the water is used for manufacturing and manufacturing processes."
  - **The new handbook gives advice on this problem**

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QA Oversight: Trending

- Trending: From the EMA Q&A
  - „Appropriate alert levels should be established based on statistical analysis of data. Trend data should be reviewed routinely and any adverse trend should be appropriately investigated. The review of trend data should not only take account the % alert and % actions occurring but also review of the quantitative and qualitative (identifications) raw data.“
  - The Aide mémoire 07121105 from German ZLG and EU GMP Guide (section 1.5 (xi.)) require trending too
- ISPE D/A/CH takes the same opinion!

➔ This brings you the valuable **process knowledge**!

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Cost comparison – what does change?

Description	WFI using membrane technology	WFI using distillation
Steam costs	Very low	Very high
Infrastructure for heat steam	Maybe not needed ➔low	High CAPEX
Measuring Technology	May be very high if EMA is followed 100%	Medium
Cost of ozone technology	High Invest, low operating costs, high maintenance/calibration	Not existing
Microbial Monitoring	High (more unit operations ➔ more sampling locations) - check sampling frequency	High

Want data for calculation? (German) Book: Fritz Röder: „Pharmawassersysteme wirtschaftlich betreiben“, page 27ff., Maas & Peither publishing, Link

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Help, HPW has been deleted!

- With the new Supplement 9.7 of Ph. Eur. HPW does not exist any more
- The EMA „Note for Guidance“ is in revision as well
  - Check your registration dossier: Is HPW mentioned? If yes, Is a supplement older than 9.7 mentioned? If yes, rely on that, write it down and keep HPW (until you want to register new products)
  - If you like to change your registration from HPW to WFI: many countries, no standardized processes (Link) ➔ will take you years

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Help, HPW has been deleted!

- If you decide to modify and requalify your existing HPW system to WFI:
  - Implement additional measuring technology
  - Change Qualification ➔ new PQ necessary?
  - Have you already written down your process control strategy? For the new EU Annex 1 you will need it anyway (and it brings you process knowledge)
  - More oversight, more control
  - More maintenance activities

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Q&A

Contact Information

Fritz Röder

Senior QA Manager

Merck KGaA, Darmstadt, Germany

Email: roederfritz@gmail.com

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