GMP-PHARMA CONGRESS

Presentation:

Implementation of cold WFI systems in Europe

Pharma Congress 2022

Facility & Technology Projects

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Düsseldorf/Neuss - Germany

PHARMA-PROCESS-ENGINEERING MULTHAUF

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Overview Content Presentation

(1) Cost for WFI

(2) Regulatory Development
USP, Japanese Pharmacopoeia,
European Pharmacopoeia, WHO

(3) Current Regulatory Troubles

(4) Technical Subjects with cold WFI:
- Ion-Exchange
- Reverse Osmosis
- Ultrafiltration

(5) Transfer / Connection to existing systems

(6) Request to use Rapid Microbial Methods (RMM) as a condition to use cold WFI-generation?

(7) Acknowledgment

(8) Copyright- & Confidentiality-Disclaimer

Price for pharmaceutical water & potential cost savings

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(Full-) Costs - with high variability:

- **Tap water = Drinking water** — **appr. 0.5 - 12 € / m³**
- **PW [&HPW]** — **appr. 5 - 30 € / m³**
- **WFI cold** — **??**
- **WFI by Distillation** — **appr. 25 - 100 € / m³**

Prices show full-costs (incl. depreciation allowance, sampling costs etc.) 2021 for central Europe, prices for drinking water incl. connected prices for waste water

Example:
Site with 500m³ WFI per day / unit HPW 15€/m³ & WFI 25€/m³ / 300 production-days per year

	cost per day [€/day]	cost per year [Mio€/year]
HPW	7.500	2,3
WFI	12.500	3,8
	saving:	**1,5**

Generation of WFI without Distillation
History - USP

Since USP23 (1995) membrane technology was allowed for WFI-Production in the US:

Water for Injection is water purified by distillation or reverse osmosis.

USP26 / 2003

U.S. Pharmacopeia
*The Standard of Quality*SM

text over time was changed to...

Water for Injection is water purified by distillation or a purification process that is equivalent or superior to distillation in the removal of chemicals and microorganisms.

USP28 / 2005 – USP41 / 2017

Generation of WFI without Distillation
History - Japan

use of UF is o.k. for more than 20 years

Water for Injection is prepared by distillation **or by reverse osmosis and/or ultrafiltration**, either: from the water which is obtained by appropriate pretreatments such as ion-exchange or reverse osmosis on Water: or from Purified Water.

When Water for Injection is prepared by the reverse osmosis and/or ultrafiltration (methods for refining water by using a reverse osmosis membrane module, an ultrafiltration membrane module capable of removing substances having molecular masses of 6,000 and above, or a module using both types of membranes), care must be taken to avoid microbial contamination of the water processing system, and to provide water with equivalent quality to that prepared by distillation consistently.

2021 Japanese Pharmacopoeia 18th Edition, JP18 official translation / https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/0000066597.html

Membrane evaluation in Europe for WFI
– a retrospective 1995 until 2017

The European Agency for the Evaluation of Medicinal Products

London, May 2002
CPMP/QWP/158/01 Revision
EMEA/CVMP/115/01 Revision

NOTE FOR GUIDANCE ON QUALITY OF WATER FOR PHARMACEUTICAL USE

The CPMP/CVMP Quality Working Party and Inspectors Working Party have recently reconsidered the use of RO water for the preparation of WFI. They have concluded on the available evidence, that the production of water by RO and associated technologies is considered to lack the robustness of distillation and concerns remain about the potential risks associated with, for example, fouling of the membrane (chemical and biological), failure of membrane integrity and lack of effective validation. Hence the current view is that Highly Purified Water is not acceptable for WFI.

New evaluation on membranes for WFI – since 2015

4. Conclusion and step forward

The Ph. Eur. WAT Working Party have concluded that there is now evidence to support a revision of the WFI monograph (0169). This revision will allow for non-distillation technologies for the production of WFI to be included in the Ph. Eur. The data to support this change are as follows:

- consistent performance of non-distillation systems;
- RO no longer used as a final stage of production;
- recognition that all water-production systems are a series of interdependent unit processes which rely on the optimum function of each stage to assure the production of water of an acceptable quality; there is a need to have successive treatments to build step-wise the water quality;
- advances in the technology and materials used for membrane production;
- 20 years of experience in non-distillation technologies;
- system design improvements to avoid dead legs and allow drainage and sanitisation;
- advances in process controls and in-line monitoring of specification parameters;
- improvements in rapid microbial methods reducing time to result;
- evidence supplied that systems are constantly meeting WFI specifications.

based on data gained with HPW in 2002 to 2013

Pharmeuropa | March 2015
Reverse osmosis in Ph. Eur. monograph Water for injections (0169)
Background document for revision of monograph Water for injections (0169), based on the Reflection Paper endorsed by the European Pharmacopoeia Commission at its 146th Session, June 2013

Update European Pharmacopeia 2017

Press Release 17 March 2016, Strasbourg, France

European Pharmacopoeia Commission adopts revised monograph on Water for Injections allowing production by non-distillation technologies

During its 154th Session held in Strasbourg on 15-16 March 2016, the European Pharmacopeia (Ph. Eur.) Commission adopted a revision of its monograph for Water for Injections (0169). Up to now, the production of Water for Injections (WFI) had been limited to distillation only. The revision allows for production of WFI by a purification process equivalent to distillation such as reverse osmosis, coupled with appropriate techniques.

...

The revised monograph for Water for Injections (0169) will be published in the Ph. Eur. Supplement 9.1 and will become effective in April 2017.

Water for injections (Aqua pro injectione)

Manufacture.

Water for injections is obtained from drinking water[1] or Purified water by distillation in an apparatus of which the parts in contact with the liquid are of neutral glass, quartz, or suitable metal and fitted with an effective device to prevent entrainment of droplets. The first portion of the distillate obtained when the apparatus begins to function is discarded. The distillate is collected and stored in conditions designed to prevent growth of microorganisms and to avoid any other contamination.

...

Other technologies proven to be equal or superior to distillation, and meeting the pharmacopoeial requirements, can be used.

Details on specific points to be conserved are outlined in the guidance on Production of water for injection by means other than distillation (***WHO Expert Committee on Specifications for Pharmaceutical Preparations...WHO Technical Report Series, No. 1025, 2020, Annex 3***).

Control Strategy and Good Practice for Production of WFI acc. WHO TRS 1025, 2020

6.6 Techniques such as deionization, electro-deionization, nanofiltration, ultrafiltration, water softening, descaling, prefiltration, degasification, and ultraviolet treatment, along with other techniques, may be **considered in conjunction with a single- or double-pass reverse osmosis system**.

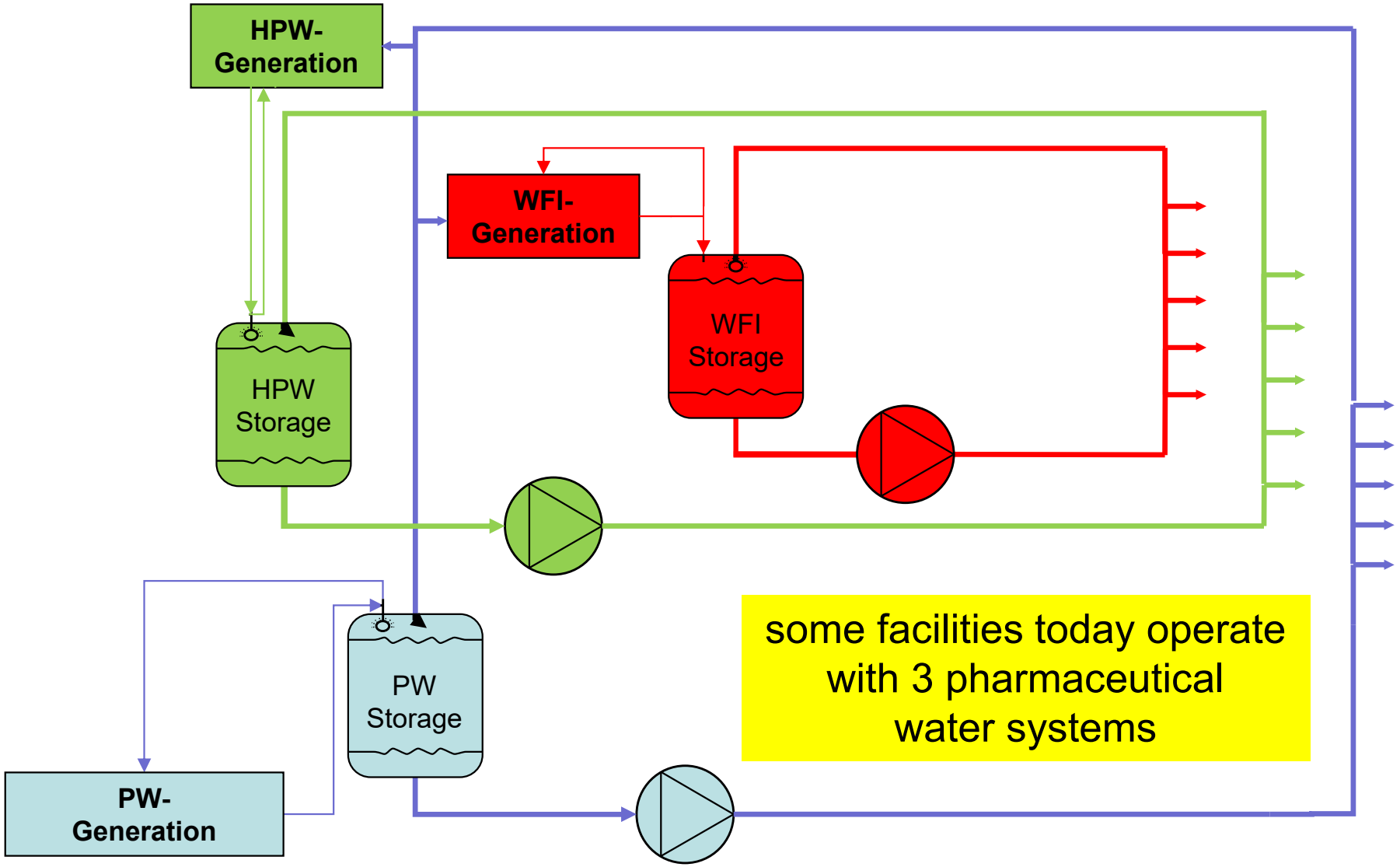
6.7 These should allow for sanitization (thermal or chemical, or a combination thereof) when required. The method of sanitization should be appropriate, effective and validated. Sanitization should be done at specified intervals, in accordance with a documented procedure.

7.4 The system should be monitored for its ongoing performance within defined parameters, including but not limited to, conductivity, total organic carbon (TOC) and microbial contamination.

7.5 A combination of online and offline monitoring of WFI should be done, to ensure that the appropriate water specification is maintained. TOC and conductivity should be monitored with online instruments. **Use of rapid microbiological methods is encouraged** for timely monitoring, and aids with rapid responses to prevent deterioration of the system.

Usual Design Utility Center with PW, HPW & WFI in Europe

today



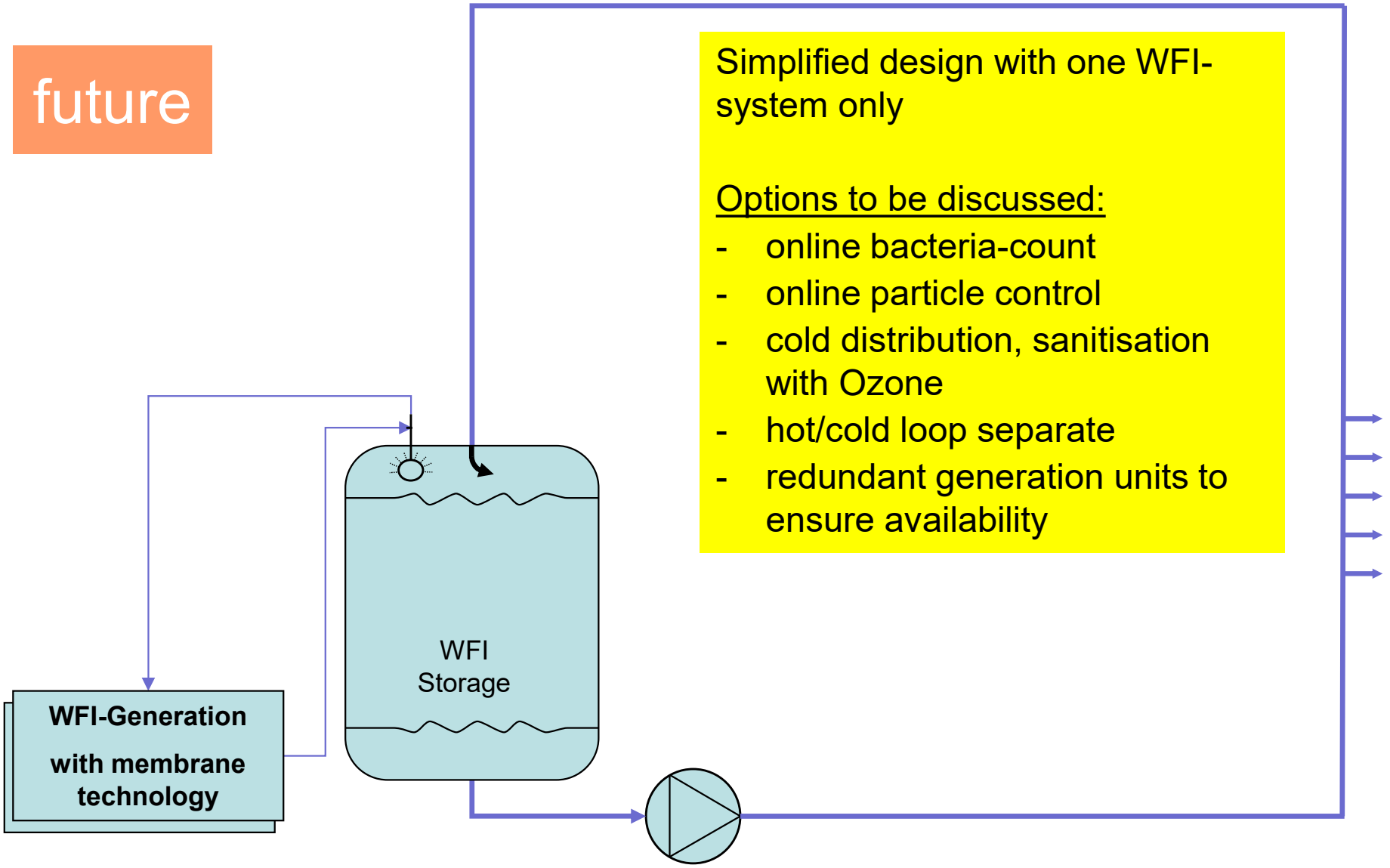
Design Future – Utility Center with (cold) WFI only

future

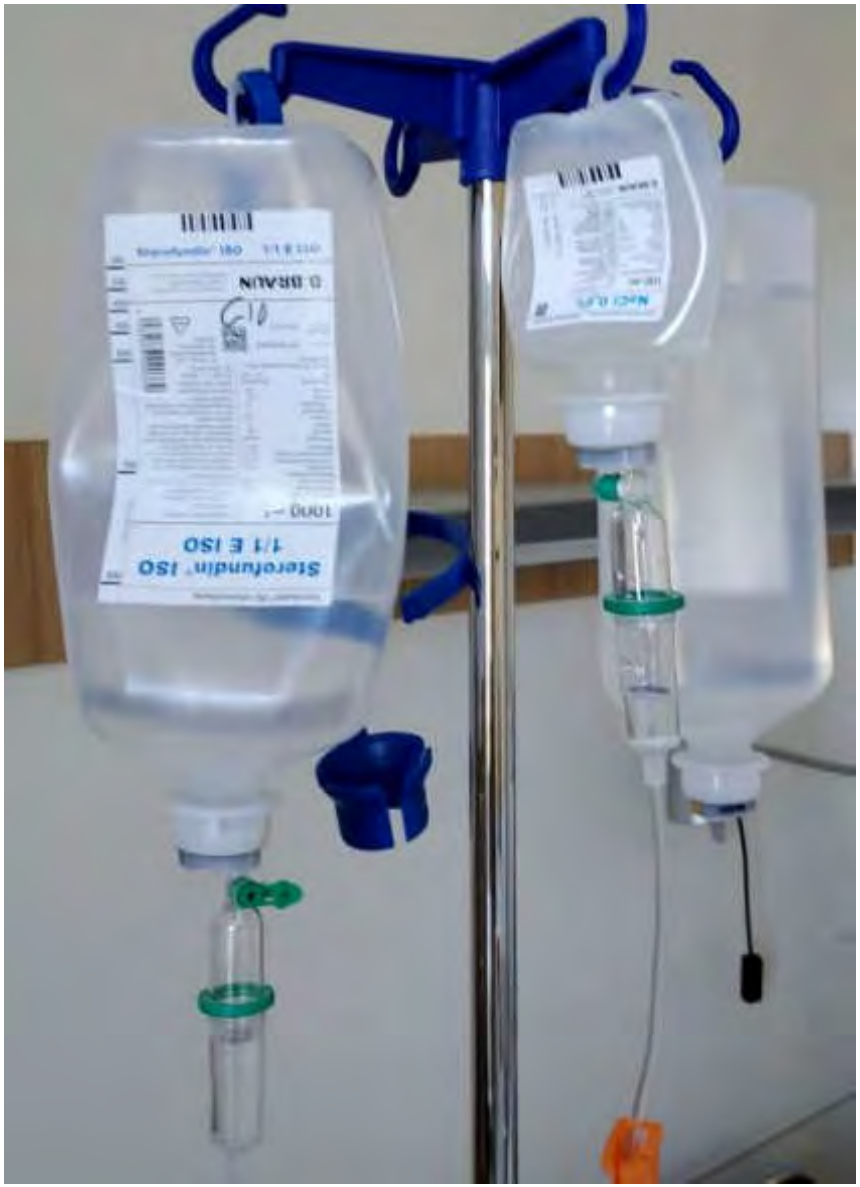
Simplified design with one WFI-system only

<u>Options to be discussed:</u>

- online bacteria-count
- online particle control
- cold distribution, sanitisation with Ozone
- hot/cold loop separate
- redundant generation units to ensure availability



Risk analysis cold “membrane” WFI + Ozone within Large Volume Parenteralia

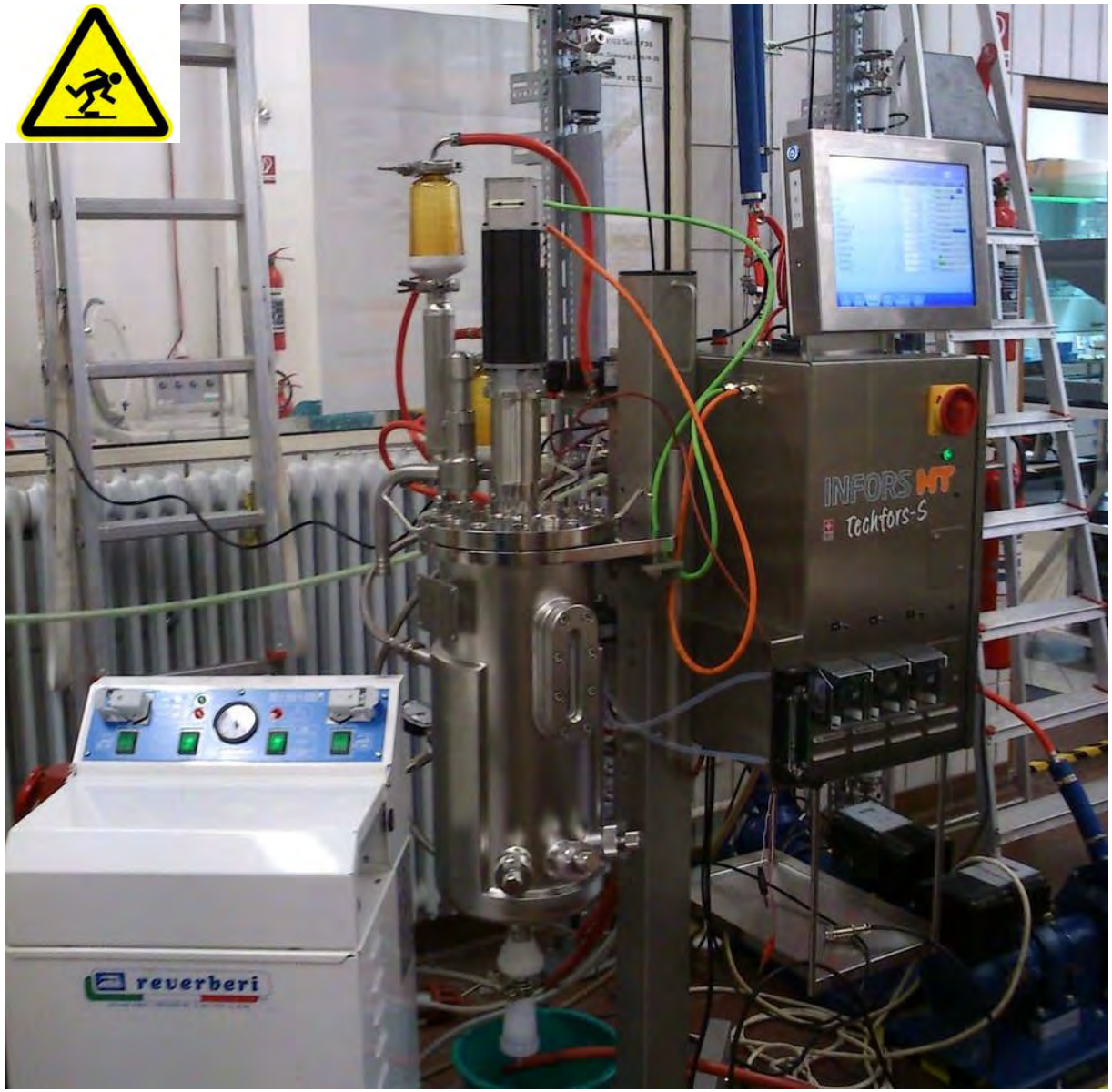


For terminally sterilized preparations

→use of cold WFI is economically a very attractive with a low risk-profile!

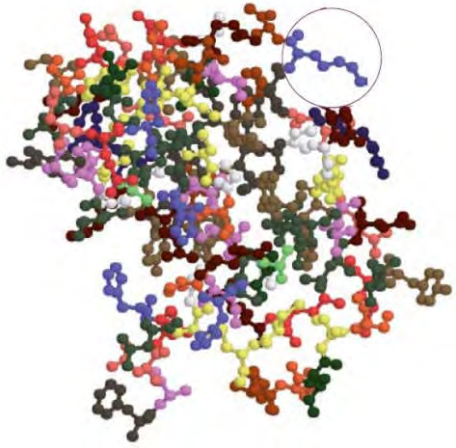
Source:
Bethesda Wuppertal Multhauf

Risk analysis cold “membrane” WFI + Ozone within Biotechnology



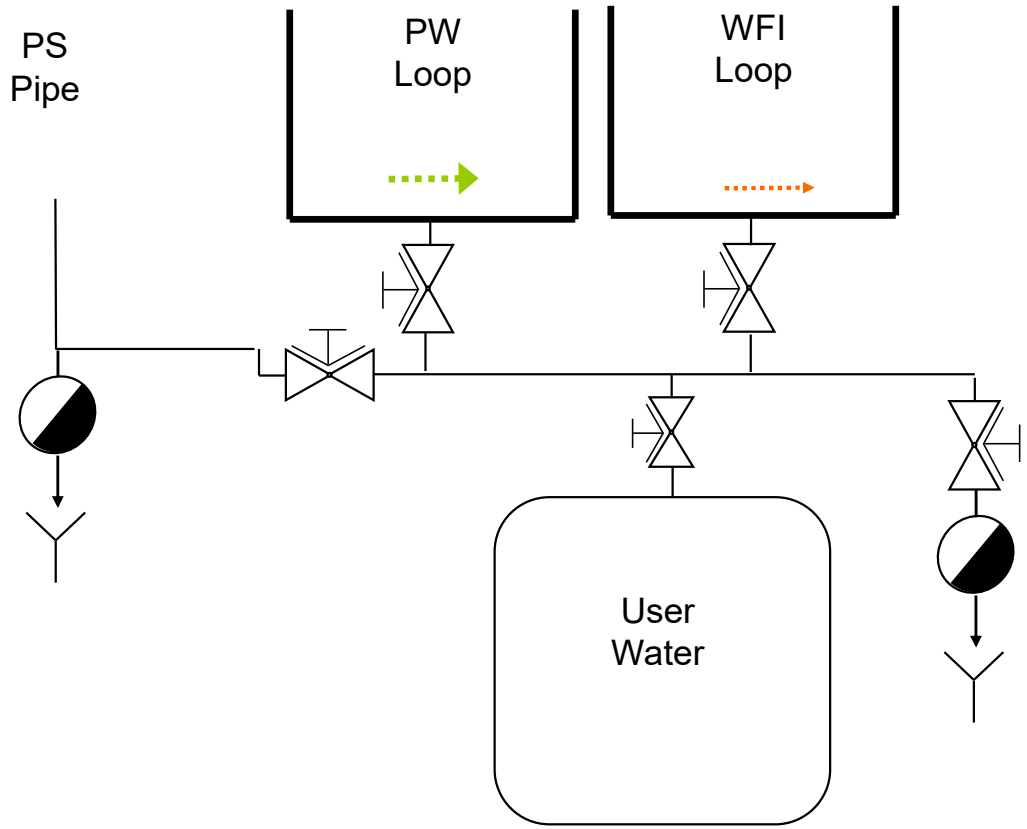
Also very interesting
due to large quantities – but...

Mammal cells like Baby Hamster Kidney-cell’s can be very sensitive against Ozone (even below 5ppb); E-Coli’s are more robust but generated biotech-products can be degenerated by Ozone, pharmaceutically critical decomposition products to be considered...



Pics:
Sanofi, 3D Insulin-model & 15 Liter Techfors S Bioreactor biochemie.uni-greifswald.de

TYPICAL for a PW- and WFI-connection to a user



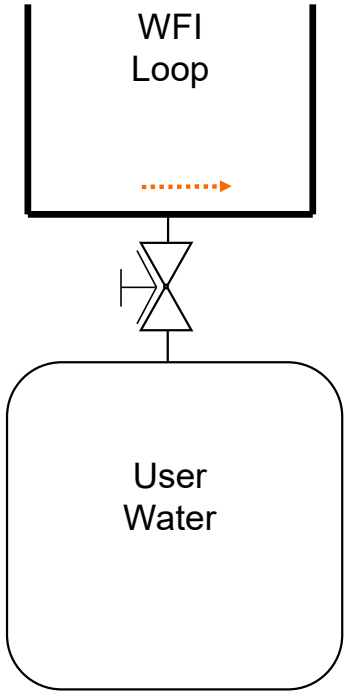
today

some users are connected to PW (for washing/CIP) and WFI (for regulatory reasons for the final rinse)

→ needs an installation with many valves & sterilisation step

Simplification with one cold WFI- System only

future



simple design with low cost for installation & low risks in operation

So, advantages are clear...

why – so many years after this regulatory change –
there are still companies that continue to produce WFI by distillation
(or, even install new WFI-distillation-plants)

???

Obstacles to implement cold-WFI-generation

(1) Not (yet) all international Pharmacopeias allow Membrane-WFI

(2) There are some very special low level regulatory hurdles – in Europe only (QA-paper, new draft Annex 1)

(3) There are some points of technical concern:
- Can bacteria grow through the UF-membrane?
- Do we really need an RO, or is Ion Exchange also o.k.?
- Wish/Request to use Rapid Microbial Methods (RMM)

WFI Quality Regulations: Japan, China & India

Japanese Pharmacopoeia XVII (2016)	
Purified Water	Water for Injection
"Water" Source; RO, UF, Deionization, Distillation, or a combination thereof	Water or Purified Water Source; Distillation or RO-UF

Indian Pharmacopoeia (2018)	
Purified Water	Water for Injections
Drinking Water Source; Dist or DI or RO or other suitable methods	Purified Water Source; Distillation or equiv/superior process

Chinese Pharmacopoeia (2015)	
Purified Water	Water for Injection
Drinking Water Source; Dist or DI or RO or other suitable methods	Purified Water Source; Distillation

Source: ISPE BG Water & Steam 3rd Ed. 2019

Distillation is also still a requirement in the International Pharmacopoeia

The major trouble-maker: QA-Paper EMA

1 August 2017
EMA/INS/GMP/443117/2017
GMP/GDP Inspectors Working Group

Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies

Final

→ highly problematic document, full of technical errors...

Evaluation of this QA-Paper by the PDA

4 November 2016

PDA Parenteral Drug Association — Connecting People, Science and Regulation®

1946 70TH ANNIVERSARY 2016

EMA
30 Churchill Place
Canary Wharf London E14 5EU
adm-gmdp@ema.europa.eu

RE: EMA/INS/GMP/489331/2016 GMP/GDP IWG
Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies

Dear Sir/Madam:

PDA appreciates the opportunity to provide feedback on this draft and fully supports the implementation of non-distillation methods for WFI production into the European regulatory framework. In addition, PDA endorses the premise that non-distillation technology for producing WFI should produce water equivalent in quality to that produced by distillation. However, PDA has concerns with many of the approaches specified in this Q&A that are not science and risk based, some of which set requirements above and beyond what is in the Pharm. Eur. Monograph.

Details: PDA uncovers mistakes in the EMA QA-Paper

Stakeholder number *(To be completed by the Agency)*	General comment (if any) PDA Parenteral Drug Association — Connecting People, Science and Regulation® — 1946 70th ANNIVERSARY 2016
	as an indication of "a must" requirement. In the context of this Q&A approach, PDA recommends the use of word "may" throughout the document as it allows practitioners to utilize risk based scientific approaches. Furthermore, the document also perpetuates the misperception that microorganisms can build up a resistance to disinfectants, and, as such, disinfectants should be rotated on a routine basis or else risk a growth of a highly-resistant organism. PDA recommends referencing pivotal evidence or illustration for this assumption. Rotation of a disinfectant and a sporicide is sufficient to significantly reduce the microbiological flora in a water system.

→ PDA error message is correct, e.g. bacteria resistant to ozone do not exist!

QA-Paper EMA vs. PDA

PDA Parenteral Drug Association — Connecting People, Science and Regulation® — 1946 70TH ANNIVERSARY 2016

Q3 76-77, 166, 176-181; Also Q5 366		Comment: The design features to allow steam use presented as requirements in this document create greater risk of contamination between steamings than a simple hot water sanitization would (e.g. no low point steam traps or steam injection points needed which could become dead legs in a water system) HW sanitization of RO is adequate as is HW sanitization of storage and distribution. Steam sanitization of storage and distribution is unnecessary, since biofilm-forming organisms in a water system are extremely susceptible to hot water temperatures (D value of 5 millisec at 80C). Proposed Change: The distribution and storage systems should be designed as to permit routine ~~steam~~ sanitisation **by steam, hot water, ozone or other** ~~with routine~~ chemicals ~~sanitization~~ and in accordance with other good design practice.

→ **PDA error message list goes on like this and is 16 pages long.**

→ Obviously, the EMA-QA-Paper is technically poor and represents a regulatory obstacle, which makes a legally compliant planning & installation of cold WFI-units difficult

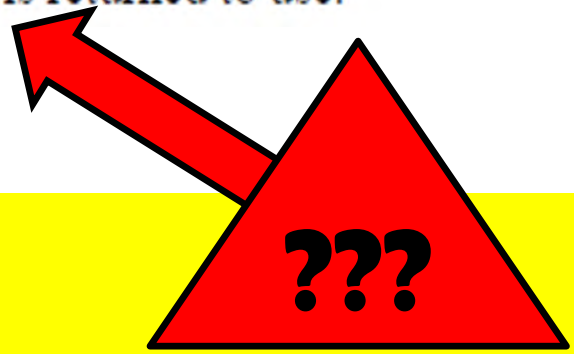
→ European inspectors unfortunately still use this QA-document as a guideline

→ EU guideline-quality-water-pharmaceutical-use & EU Draft Annex 1 from 2021 are using this faulty QA-paper as reference

Other Problem with Regulations
EU Draft Annex 1

6.12 To minimize the risk of biofilm formation, sterilization or disinfection or regeneration of water systems should be carried out according to a predetermined schedule and when microbial counts exceed action limits. Disinfection of a water system with chemicals should be followed by a validated rinsing/flushing procedure. Water should be tested after disinfection/regeneration. The results should be approved before the water system is returned to use.

source: 2021 / https://ec.europa.eu/health/sites/health/files/files/gmp/2020_annex1ps_sterile_medicinal_products_en.pdf



Problem 1:

Do we have biofilms in WFI-systems?

Problem 2:

Disinfection with chemicals can not remove bacteria from many types of water treatment systems → thermal sanitisation is state of the art for all HPW-plants

Problem 3:

Wait for MiBi-results after every disinfection / sanitisation – with plate count??

Statement EMA about our concerns with the QA-paper for cold WFI & new Draft Annex 1

...

So as I understand it, there is a good deal of flexibility in this Q&A that leaves critical decision making with the manufacturer. The key for the manufacturer is that they make their decisions based on good science and engineering and be able to convince the regulatory authority that their system as designed and the contamination control strategy as implemented will produce or produces WFI of EP grade and prevents the growth of microorganisms and biofilm proliferation. QRM can be used in the decision making. As with any guidance alternative approaches can be utilized by the manufacturer provided there is sound justification.

The Q&A notes that "This set of questions and answers is intended to provide preliminary guidance until such time the on- going revision of Annex I of the GMP guide is complete" and as Annex 1 is currently being developed we are currently looking how we take the Q&A forward.

I hope that this addresses your comments.

Brendan Cuddy
Head of Manufacturing Quality and Supply Chain Integrity,
Committees & Inspections Department
European Medicines Agency
Domenico Scarlattilaan 6 | 1083 HS Amsterdam | The Netherlands

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We're moving! For details, see How to find us.

from: EMail Mr. Cuddy to M.Multhauf / Subject RE: EMA QA-paper WFI by non-distillation methods "full of technical and logical mistakes" will be invalidated when GMP-Annex 1 is final? / 12th June 2019

Problem:
Who defines the state of the art and how?

PHARMACEUTICAL ONLINE

Guest Column | October 11, 2019

ISO 22519: An Unnecessary, Faulty, And Confusing Standard

Recently, the *PDA Letter* published an article titled "ISO 22519: A Flawed and Counterproductive Standard."[1] The authors of this article pledged to continue educating industry about deeply flawed ISO Standard 22519,[2] which claims to be the new word in purified water (PW) compliance. In fact, this standard neither promotes innovation nor compliance. On the contrary, it brings confusion to those that are embarking on purified water production and use in the pharmaceutical industry. The main proponent of the standard, which effectively acts as a vehicle for the promotion of the proponent's patented pretreatment technology, is a single manufacturer and its allies. Furthermore, the standard was prepared in the ISO Water Reuse Committee, which has nothing to do with pharmaceutical water.

ISO 22519:2019 Purified water and water for injection pretreatment and production systems; www.iso.org

Pharmaceuticalonline.com, Guest Column October 11, 2019, ISO 22519: An Unnecessary, Faulty, And Confusing Standard

Conclusion on regulation and the state of the art

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Confusing times for new non-destillation-WFI-generation systems...

If a company puts compliance over

- ***science &***
- ***economy &***
- ***efficiency &***
- ***ecology***

then this company has to keep the old steam-pot technology

Generation of WFI by Ion Exchange + Ultrafiltration ??

- Only Technology, where almost 100% of the feed water is desalinated
- Low operation cost
- Used with high quality raw water sources
- Reliable technology

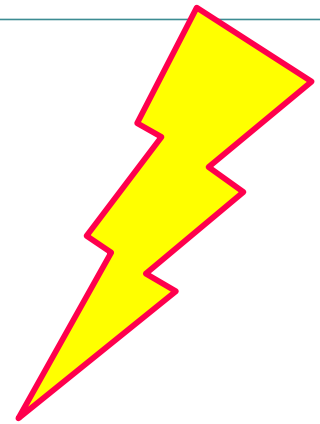
Picture H+E-IE-plant installed in a large volume Parenteral Site

in Europe, we have some large sites producing HPW (some 100m³ per day) via Ion-Exchange + UF successfully since more than 15 years

Remark WFI by Ion Exchange / European Federation of Pharmaceutical Industries and Associations

- all those HPW-plants are now under discussion – because an upgrade to WFI is not clear - regulatory compliance is under discussion

- downgrade to PW with Endotoxin-Limit is difficult – some HPW-applications now require WFI



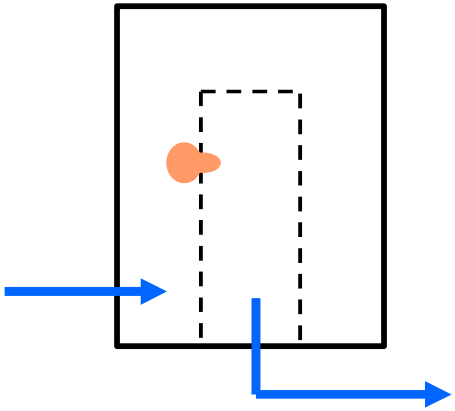
Tightening up the requirements from potable water to purified water and from purified water to WFI will increase environmental burden due to the additional potable water consumed to produce Purified Water and WFI. ...The proposed increase in requirements for water quality will increase the consumption of water **putting some production sites at risk for insufficient availability of water**, indeed already constituting a threat to some sites with the current water consumption.

Apart from the extra burden of cost and environmental impact, the blanket adoption of more stringent requirements for water quality **will not provide any further benefit to patients regarding safety, quality, efficacy or potency.**

Source yellow comment: 2019 European Federation of Pharmaceutical Industries and Associations
https://www.efpia.eu/media/412839/efpia-comments_guideline-on-the-quality-of-water-for-pharmaceutial-use_final130519.docx

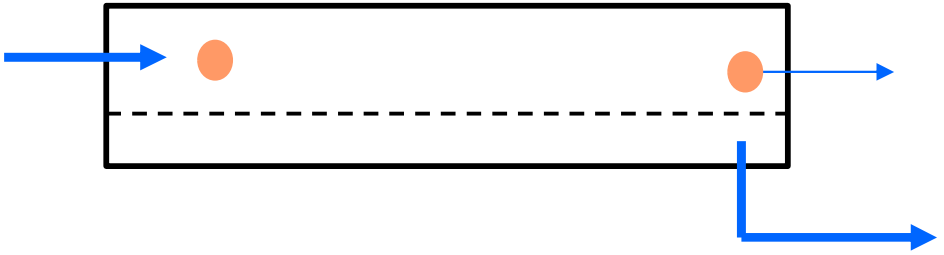
Ultrafiltration (UF) – dead end vs. cross-flow

Don’t mix it up - even, if the name and/or the membrane-MWCO is the same, the process design makes the difference....



organic material is pushed into the membrane,
high risk of break-trough due to shape-adaption

2T€



organic material is flushed out (taking the „easy way“)

10T€

Ultrafiltration (UF) – Risk with Dead End

Note on Dead-end Filtration

Dead-end filtration (100% recovery of feed water as product) may cause an air buildup in the upper part of the module. This could lead to membrane drying and prevent normal filtration performance.
Dead-end filtration may also cause quick fouling of UF membrane by particulates and/or bacteria and the membrane may lose filtration ability.
Pay attention to following items if recovery rate comes closer to 100%.

From Operation Manual ASHAI Microza OLT-6036HA_en / April, 2012

Options for UF – Sanitisation

There is still some concern that bacteria can grow through the UF membrane.
To counter this, the following options have been developed:

- **Continuous UF Sanitisation:**
  - adding ozone before the UF (for ceramic modules only)
  - heating the WFI after EDI before UF to 60-80°C (for systems with hot storage & distribution)

- **Discontinuous UF Sanitisation**
  e.g. every night / for 2-4hrs per day / week
  - circulation of ozonated water from the cold-WFI storage (with 20-50ppb)
  - circulation of hot water from the hot WFI storage

Example: Transformation Strategy
PW & WFI Generation – Starting Point

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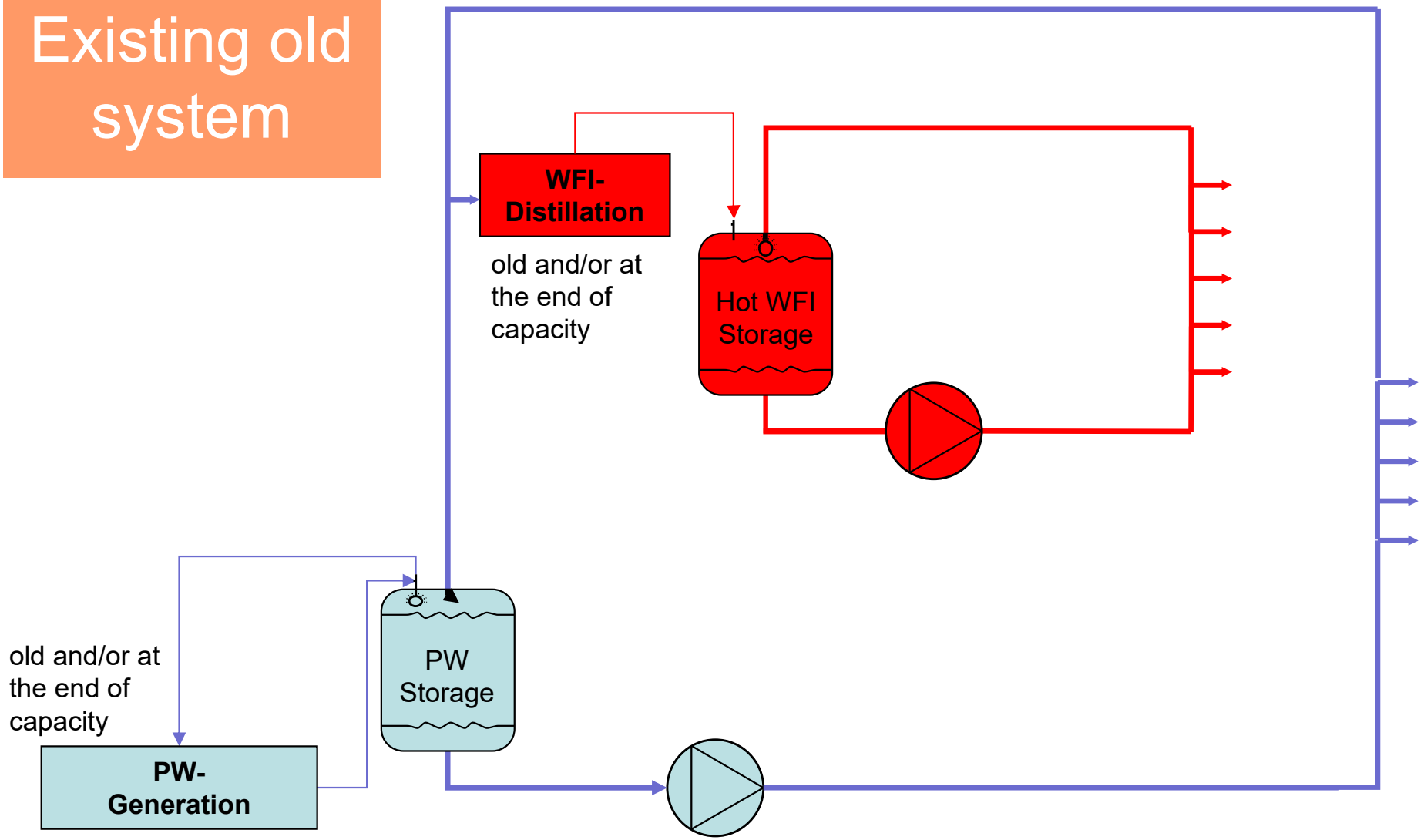
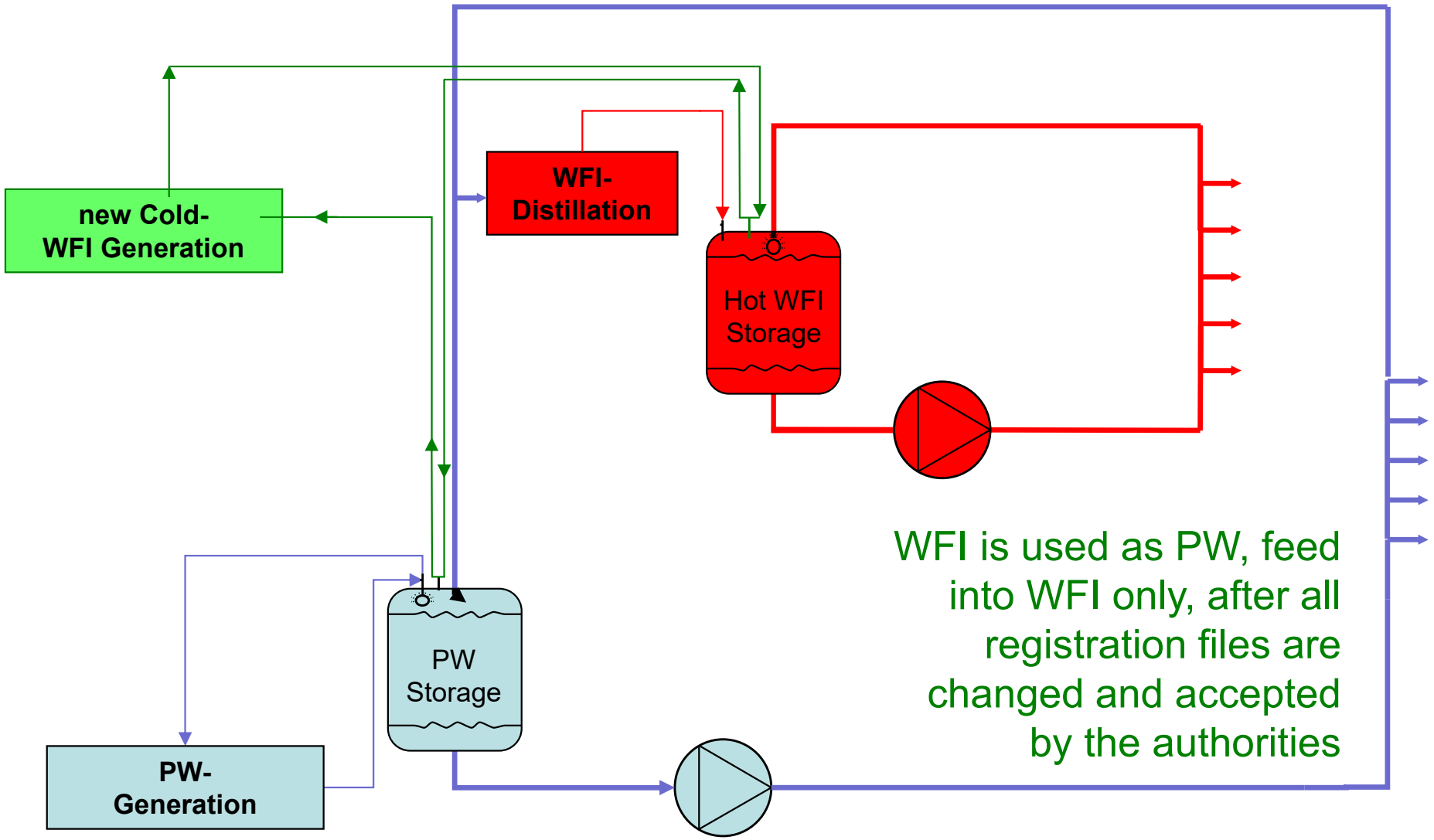
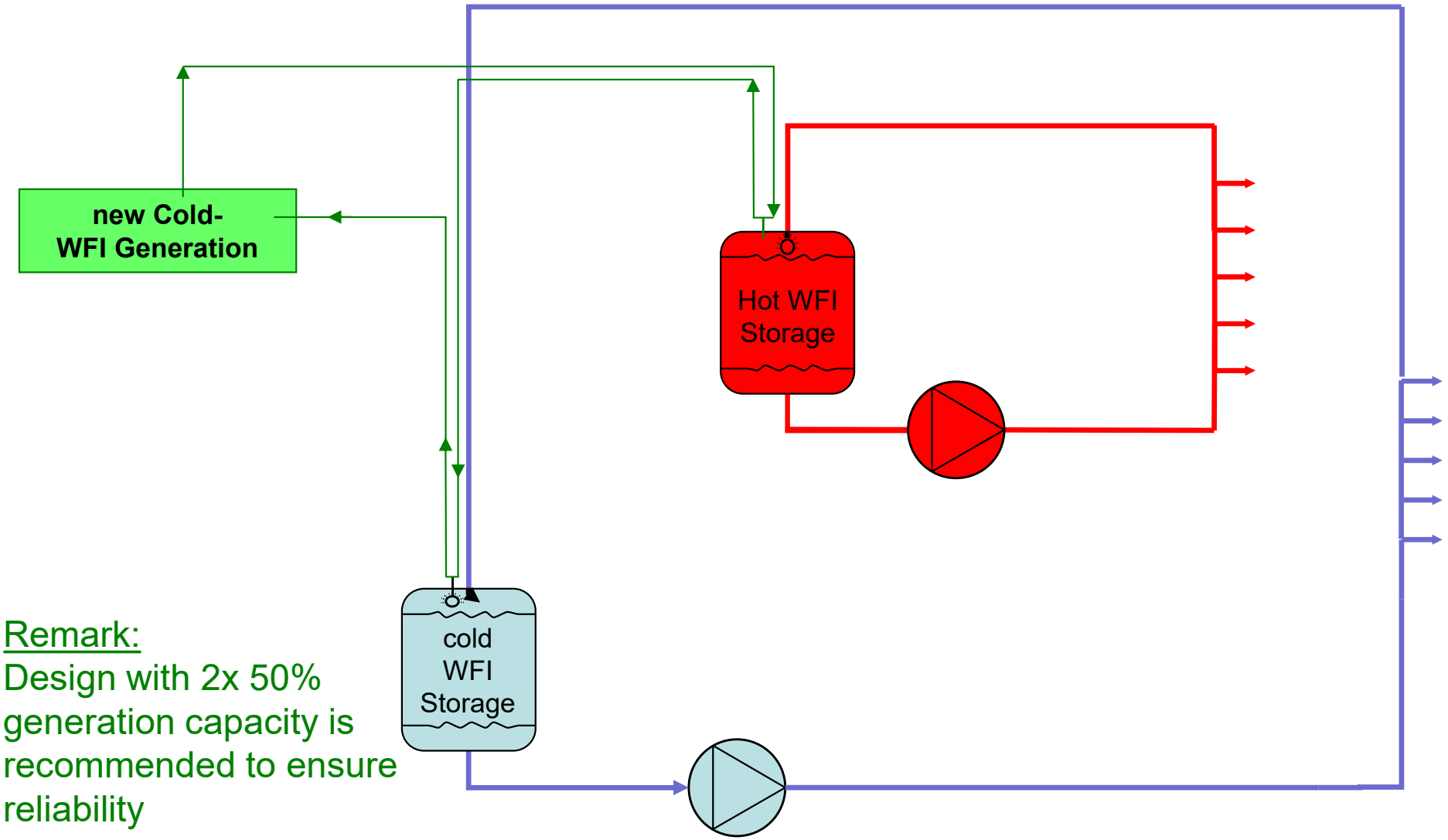
Existing old system



Step 1 with new cold WFI, Transition phase



Step 2 with new cold WFI, final design



Remark:
Design with 2x 50% generation capacity is recommended to ensure reliability

Request to use
Rapid Microbial Methods (RMM)- Online-MiBi-Units

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6. What testing should be employed during initial qualification and routine operation sampling?

Testing should be conducted in line with Ph.Eur. Monograph 169 'Water for Injections'.

Use of rapid microbiological methods should be considered as part of the control strategy to aid with rapid responses to deterioration of the system.

Article 23 of Directive 2001/83/EC states "...the authorisation holder must, in respect of the methods of manufacture and control...take account of scientific and technical progress..."

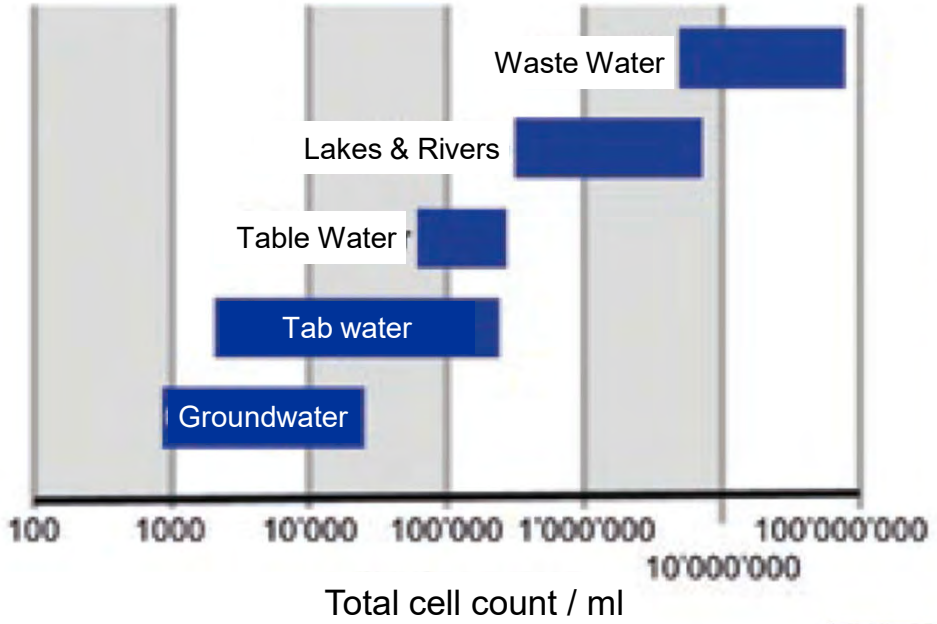
Methods to be considered should include:

- Rapid Endotoxin testing – use of more sensitive and point of use test methods.
- Quantitative microbiological test methods – in line with Ph.Eur. 5.1.6 monograph 'Alternative Methods for control of Microbiological Quality'.

Some inspectors interpret this QA-paper & the WHO TRS 1025 that cold WFI manufacturing is only allowed if one is installing also a online MiBi monitoring?!??!

Source: Questions and answers on production of water for injections by non-distillation methods – reverse osmosis and biofilms and control strategies EMA/INS/GMP/443117/2017 GMP/GDP Inspectors Working Group

CFU-counts vs. RMM with Flow Cytometry – Example Drinking Water City of Zurich



Flow Cytometry allows the detection of all cells present, including those that would not grow into colonies on nutrient plates [...].

The drinking water of the city of Zurich does not have between **0 and 10 CFU/ml** [...] but usually between **80'000 and 150'000 cells/ml.**

Source Diagram, Pic. [Flow cytometry test in MiBi-lab] and Text: Public Drinking Water Supply Zurich CH 2017; Das kleine Einmaleins der Trinkwasserkeime [by Wasserversorgung Zürich] / translated

Major Issue with the use & results of Rapid Microbial Methods (RMM)- Online-MiBi-Units

USP 1223

Encourages validation of alternative Rapid Microbial Methods (RMM)

Ph.Eur. 5.1.6.

Alternative Methods for Control of Microbiological Quality

Validation of comparability is required to use the RMM for product release -

But: **Comparability of the CFU values with the new measured values is not possible / realistic**

e.g. because viable but non culturable (VBNC) bacteria's are not found with the CFU-method – but with RMM's we find them & we know, many critical bacteria in our PW and WFI are VBNC).

→ Pharmacopoeias need to be revised to show ways out of this dilemma.

Online-MiBi:
Values Biovigilant - IMD-W

Pic.: Biovigilant / PMT - IMD-W

Figure 4-6 IMD-W Graphing Colors on the Measure Screen Chart

Conclusion RMM‘s / Online-MiBi-Units – why they are not "state of the art”

Devices are currently not a simplification of MiBi-quality assurance for PW or WFI

High bacterial counts measured are problematic – generating CAPA’s & Deviations and never ending discussions about the necessity to perform additional CFU analyses & identification analysis

Identification of these “newly recognized” MO’s can’t be done "besides" the normal daily work of a pharmaceutical MiBi laboratory
→ real scientific basic research is required to solve this issue
→ maybe new RMM-units are required, which are capable to quantify & identify bacteria at the same time

Conclusion for RMM & Cold WFI

A requirement to have always an online MiBi-unit for cold-WFI-generation systems is highly questionable / has to be rejected.

Conclusion RMM / Online-MiBi- why they can nevertheless already be useful today

1) Deviation-Management
In the case of CFU-findings, the data from the online device can be checked - and a decision can be made on the basis of the data as to whether the plants were actually "out of range".

2) Havoc-Management
After malfunctions, e.g. pump or power failures, it would be easier to make decisions: e.g. must tank be emptied & refilled? must be sanitized? - faster release system for production after disturbances

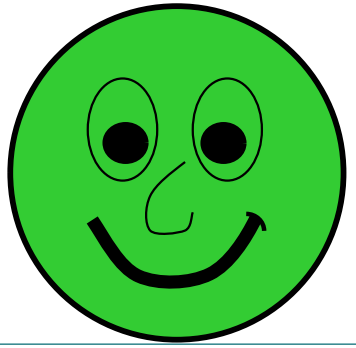
3) Definition of the Sanitisation-Cycles
Data-based decision on the timing and frequency of sanitizations become possible.

4) Detail-Trending & Operation-Optimisation
CFU sampling is always only a snapshot. Online MiBi could be used to record untypical peaks - e.g. during valve switching / flushing / recirculation over the weekend, etc. - and optimize the systems if necessary (extend flushing cycles until values return to normal, etc.).

5) Quantify “house germs” in the systems & identify if necessary.
MiBi analyses are no longer a "blind cow" game, but are based on real data. Prerequisite e.g. for "yes, germ found, but is not critical for the product".

6) Optimize CFU sampling & analysis
E.g. clearly determine "worst case" in terms of time and place, possibly combined with the possibility of reducing the number of CFU analyses.

7) Option: Record parallel Particle-values
Could be a help with error analysis for particles found in pharmaceutical formulations



Conclusion about the Implementation of cold WFI systems in Europe

- **Regulatory troubles for this subject are not over yet**
- **Cold-WFI-generation projects have some special technical risks**
- **Nevertheless there are appr. 20 cold WFI-generation units already installed & appr. 50 more are on the way for 2022 & 2023 - in Europe alone**
- **The end of the WFI distillation in Pharma- & Biotec-Production-plants is gaining momentum – also worldwide**

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