STERIS
Life Sciences

Draft Annex 1 and What it Means to Sterilization and Moist Steam Quality

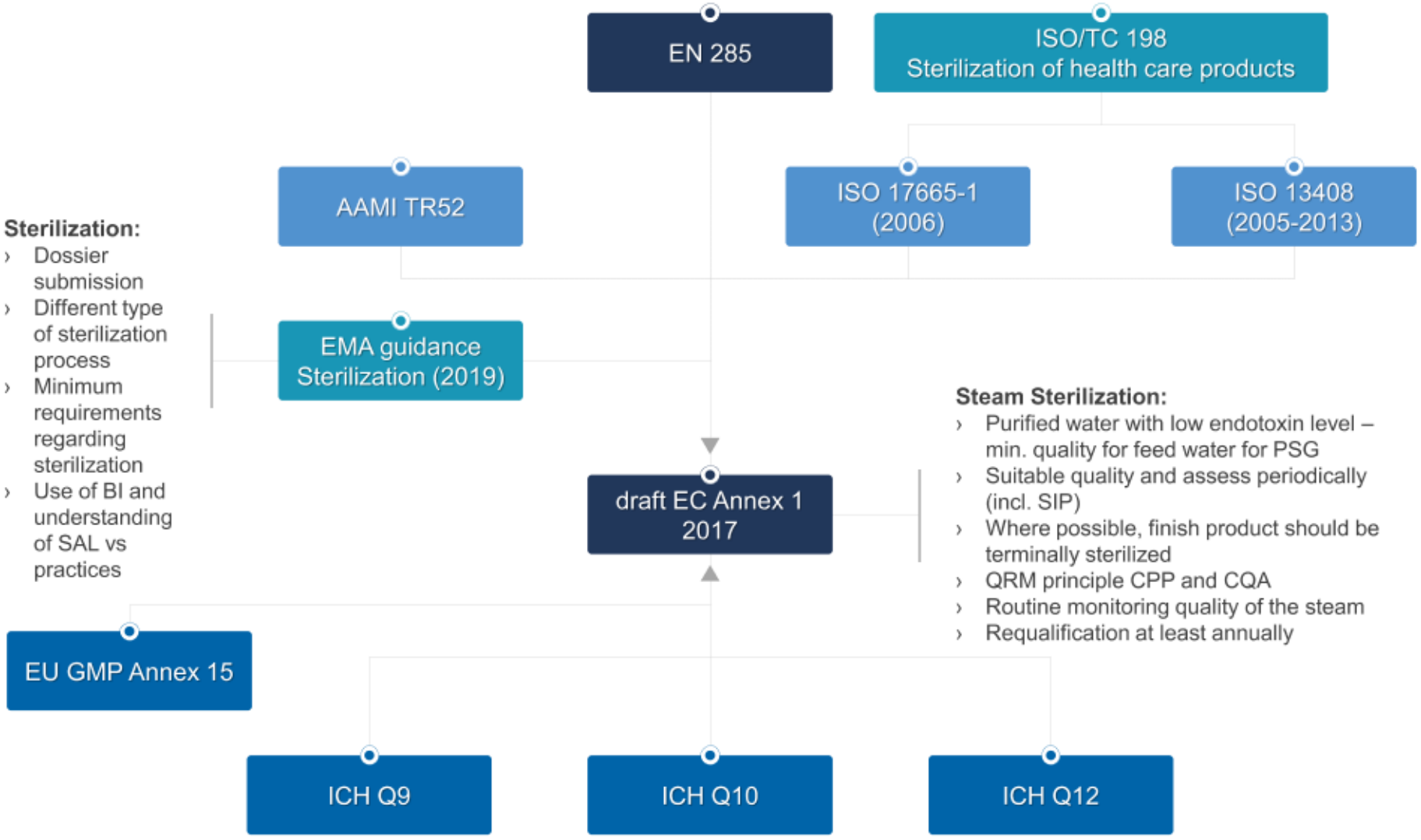
Walid El Azab
Technical Service Manager
+32479790273
Walid_elazab@steris.com

Science & Solutions for Life

Agenda

1. Regulatory aspect and link
2. Sterilization and Moist Steam Quality vs draft Annex 1
3. Common mistakes observed
4. Conclusion and Q&A

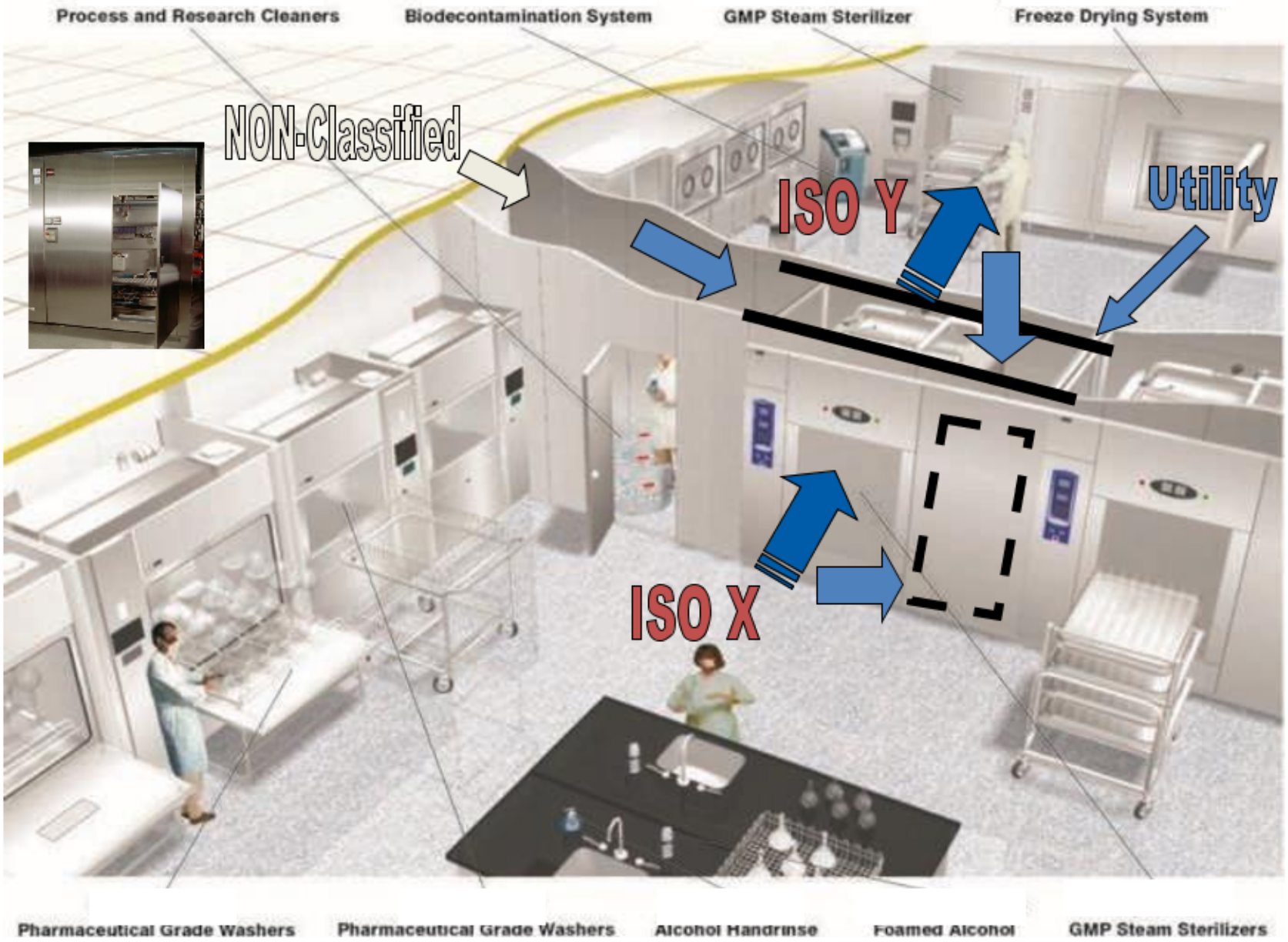
Requirements for steam used for sterilization will be addressed in the future Annex 1



NON EXHAUSTIVE

The selection, design and location of the equipment used for sterilization should be decided using QRM principles.

STERIS
Life Sciences



The design of the cycle/programme used for sterilization should be decided using QRM principles

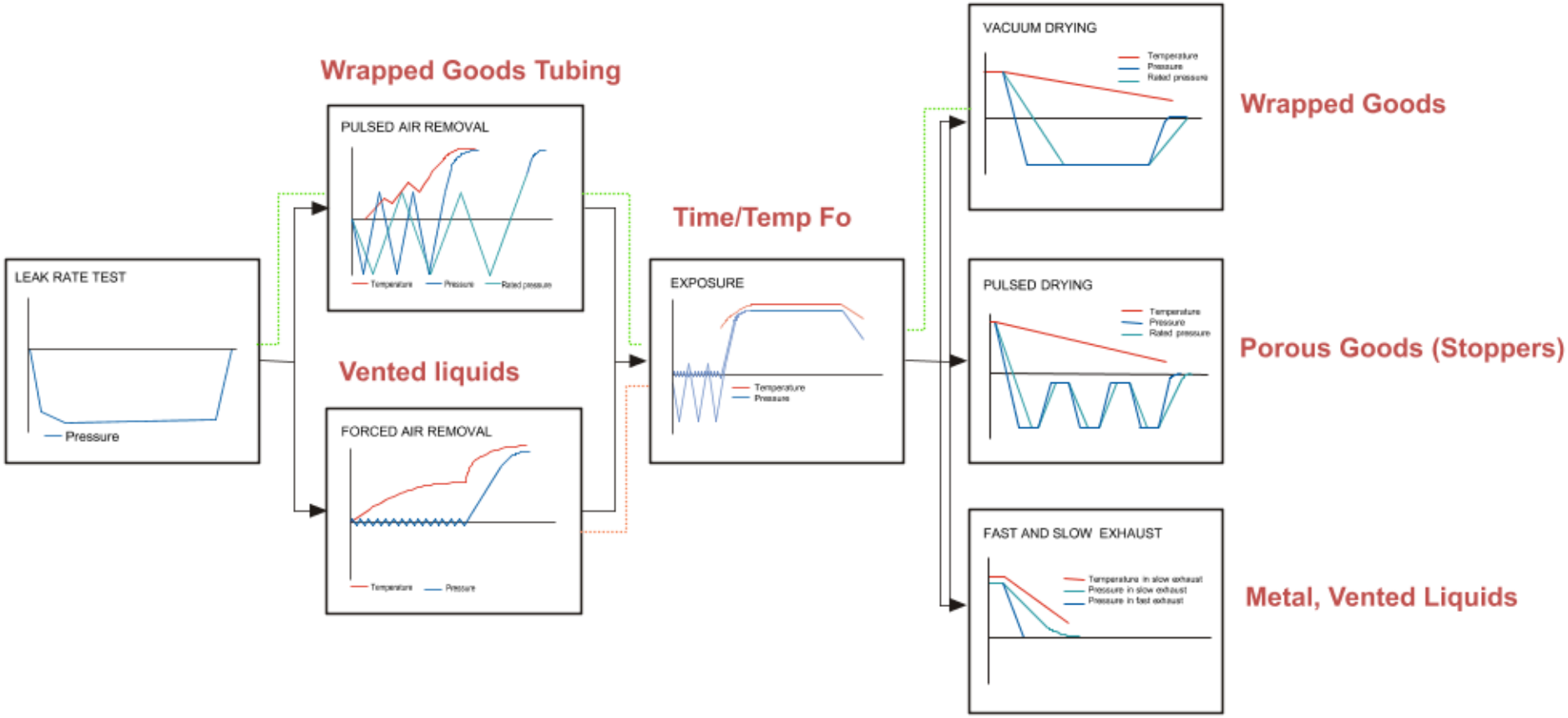
STERIS
Life Sciences

Pre-Cycle

Pre-Conditioning

Exposure

Post-Conditioning



Particular attention should be given when the adopted sterilization method is not described in the current edition of the Pharmacopoeia

STERIS Life Sciences

Table 1 Cycles for steam sterilisation and post-aseptic processing terminal heat treatment and corresponding data required in the quality dossier

Cycle	Type of process	Information in dossier*	Bioburden level before steam sterilisation or terminal heat treatment	Bioburden Characterised	Process hold temperature
Ph. Eur. 5.1.1 Reference Cycle	Sterilisation	1, 6	100 CFU/100ml (non-routine)	No	≥ 121 °C for ≥15 minutes
Overkill cycle F_o >12 min	Sterilisation	1, 2, 3, 4, 7	100 CFU/100ml (non-routine)	No	≥ 121 °C
F_o > 8 min	Sterilisation	1, 2, 3, 4, 7	100 CFU/100ml (routine)	No	> 115 °C
F_o > 8 min	Sterilisation	1, 2, 3, 5, 7, 8	100 CFU/100ml (routine)	Yes**	> 115 °C
F_o > 8 min	Sterilisation	1, 2, 3, 4, 7	100 CFU/100ml (routine)	Yes	> 110 °C
F_o > 8 min	Sterilisation	1, 2, 3, 5, 7, 8	100 CFU/100ml (routine)	Yes**	> 110 °C
F_o <8 min	Post-aseptic processing terminal heat treatment	1, 2, 3, 4, 7, 8	0 CFU/100ml, aseptic filtration and processing prior to terminal heat treatment (routine)	Yes***	> 110 °C****
F_o <8 min	Post-aseptic processing terminal heat treatment	1 2, 3, 5, 7, 8	0 CFU/100ml, aseptic filtration and processing prior to terminal heat treatment (routine)	Yes***	> 110 °C****

* For clarification of the code numbers, see below

** In-process control demonstrating acceptable heat resistance of bioburden

*** The bioburden prior to the sterilisation step (i.e. filtration) should be characterised for heat resistance

**** Temperatures below 110 °C may be used if justified. The requirement for additional documentation for such cycles is evaluated on a case by case basis

Top consideration when validating an autoclave

STERIS
Life Sciences

Top Consideration

1. Sterilization cycle
2. Load configuration
3. Worst case load and location
4. Choosing the right control for liquid
5. Thermocouple wire
6. Acceptance criteria
7. Thermocouple accuracy verification
8. Document the validation test runs
9. SOP and Training tools
10. Project planning
11. Control and on-going monitoring

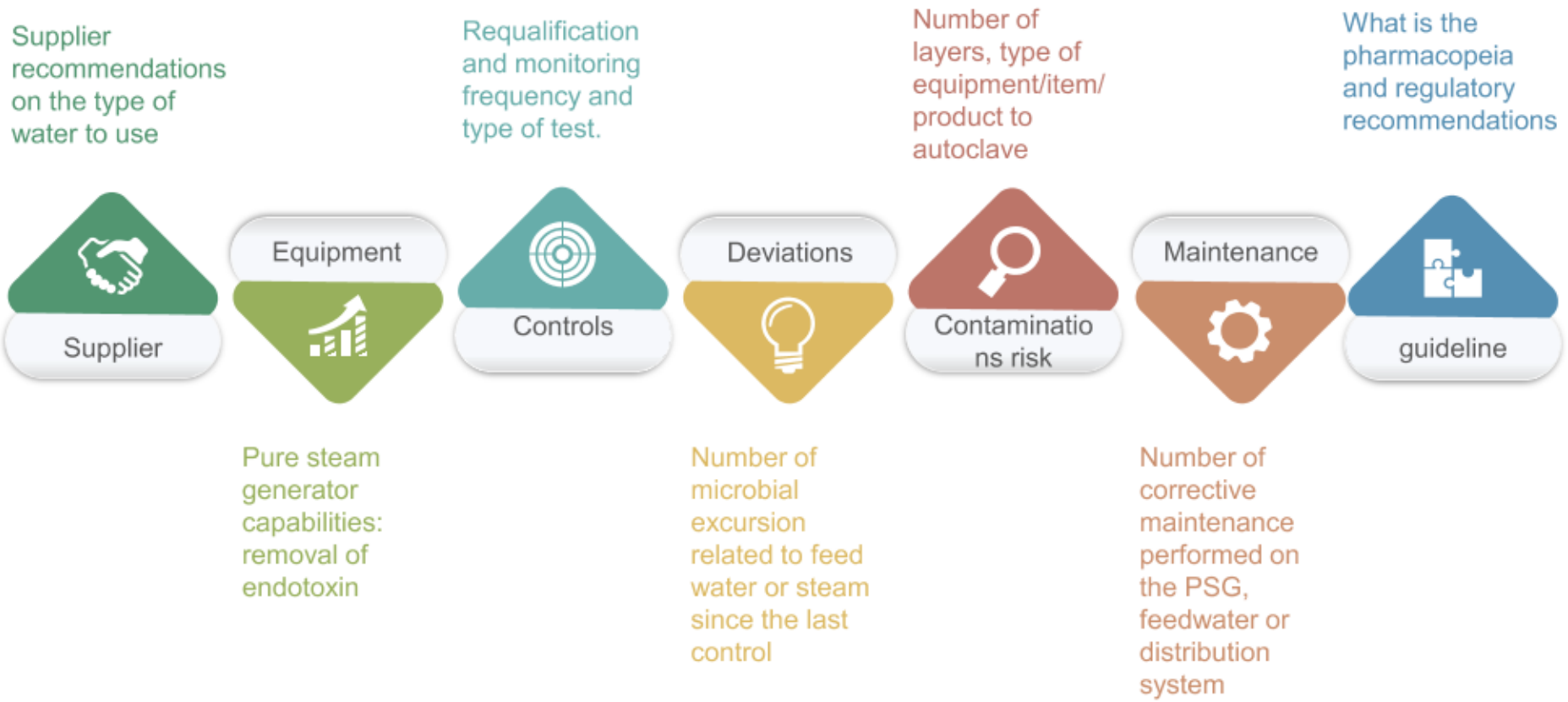
Parameters to understand and control

The draft Annex 1 (2017) suggest that

STERIS Life Sciences

"purified water, with a low level of endotoxin, should be used as the minimum quality of feed water for pure steam generator."

➔ The minimum quality of feed water for PSG should be justified based on a QRA:

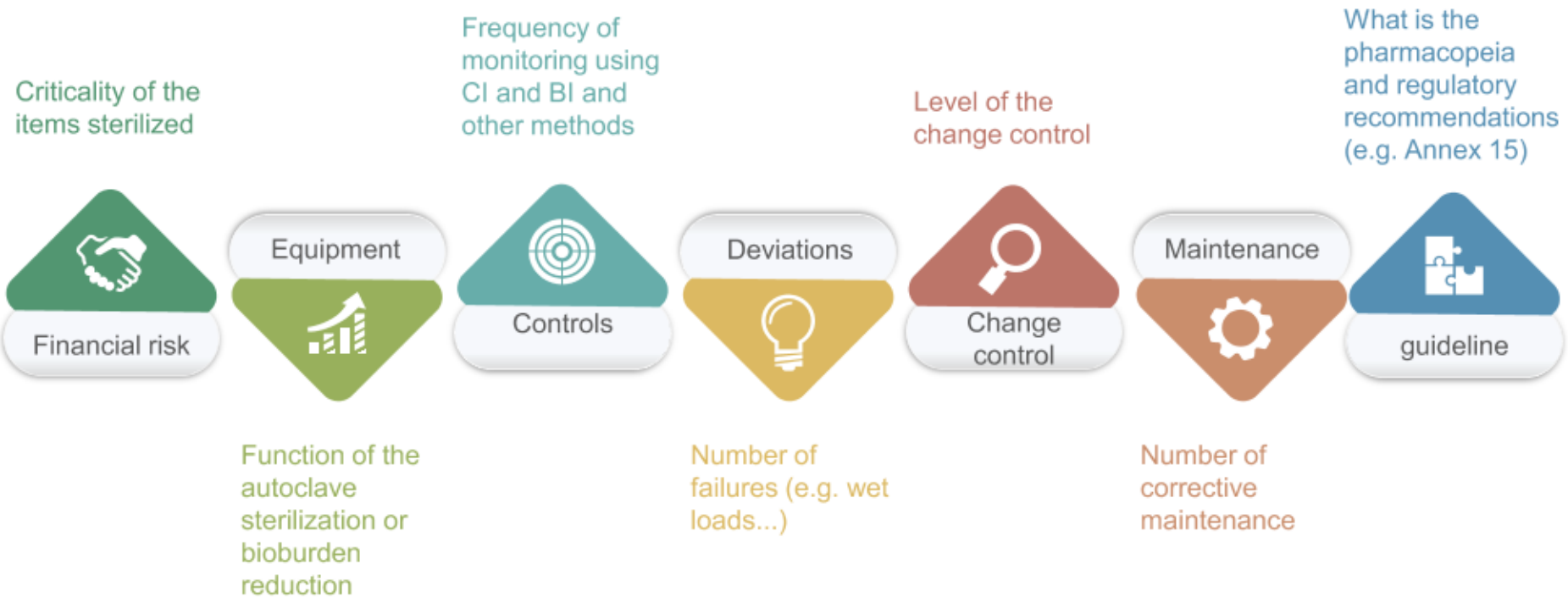


Proposed changed: "The minimum feed water for the pure steam generator should comply with the appropriate pharmacopeial pure steam monograph. However, when the risk of endotoxin contamination is identified then a higher water quality should be required."

The draft Annex 1 (2017) suggest that…

"The validity of the process should be verified at scheduled intervals, with a minimum of at least annually."

➔ the frequency of the sterilization process validity be justified upon a QRM approach



Quality of steam used for sterilization – draft Annex 1 (2017)

STERIS
Life Sciences

- ✓ Quality of steam should include consideration of the following examples:
  - ✓ non-condensable gases,
  - ✓ dryness value (dryness fraction),
  - ✓ superheat
  - ✓ steam condensate quality.

The draft Annex 1 (2017) suggest that…

"the quality of the steam used for sterilization should be assessed periodically against validated parameters."

The validity of the process should be verified at scheduled intervals, with a minimum of at least annually

STERIS Life Sciences

1. **Steam quality** is determined through physical, chemical and endotoxin testing. Tests include (EN285 (2015) & HTM-01-01 part C 2016 standard):
   - non-condensable gases: dry saturated steam containing not more than 3.5% v/v of non-condensable gases.
   - superheat: The degrees of superheat measured in free steam at atmospheric pressure shall not exceed 25° C.
   - dryness value : dryness value of not less than 0.9 (for metal loads not less than 0.95)
2. **Temperature mapping** to verify uniform distribution of heating medium across load zone, test include :
   - Empty chamber (+/-0.5 °C)
   - Loaded chamber (1-2 ° C)
3. **Probe calibration**
4. **Inline filter** to be replaced at a determine frequency

Source photo: http://www.copybook.com/img/pgib3884s6679/steam-quality-test-kit-components.jpg

The validity of the process should be verified at scheduled intervals, with a minimum of at least annually

STERIS
Life Sciences

Steam quality requirements

3.74 The requirements in Table 5 should be met when measuring the quality of steam.

Table 5 Specification for contaminants in condensate collected according to the method described in BS EN 285

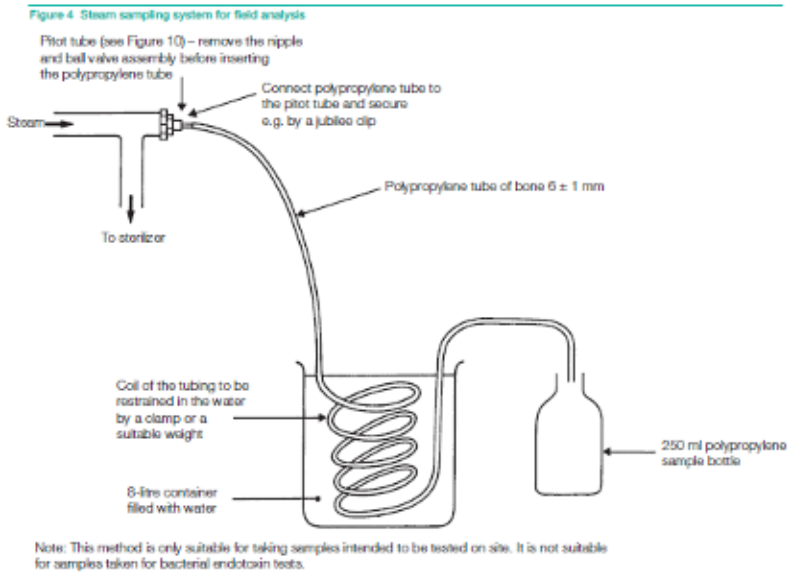
Physical qualities:	
Dryness	≥0.95
NCG	≤3.5%
Superheat	≤25C
Particulate qualities:	
Silicate	≤0.1 mg/L (corrosion)
Heavy metals	≤0.1 mg/L (corrosion and load)
Cadmium	≤0.005 mg/L (corrosion)
Lead	≤0.05 mg/L (corrosion)
Chloride	≤0.1 mg/L (corrosion), ≤0.5 mg/L (load)
Phosphate	≤0.1 mg/L (corrosion and load)
Conductivity	≤3 µS/cm (corrosion), ≤35 µS/cm (load)
pH	5–7 (corrosion)
Hardness	≤0.02 mmol/L (corrosion)
Appearance	clear, colourless, no sediment (corrosion), clear and colourless (load)
Endotoxins	≤0.25 EU/mL (load)
Ammonium	≤0.2 mg/L (load)
Nitrate	≤0.2 mg/L (load)
Sulphate	Ra (load)
Oxidisable Sub	Ra (load)
Evap Residue	≤30 mg/L (load)
Calcium & magnesium	Ra (load)
NOTE: This table is a combination of tables A1 (re: corrosion) and A2 (re: load) in BS EN ISO 17665 and BS EN 285. Compliance with this Table addresses the issues of equipment corrosion and load contamination.	
NOTE: Ra signifies methods and reagents specified in the European Pharmacopoeia	

Source: HTM-01-01 part C: Steam Sterilization (2016)

Steam sampling system for field analysis

STERIS
Life Sciences

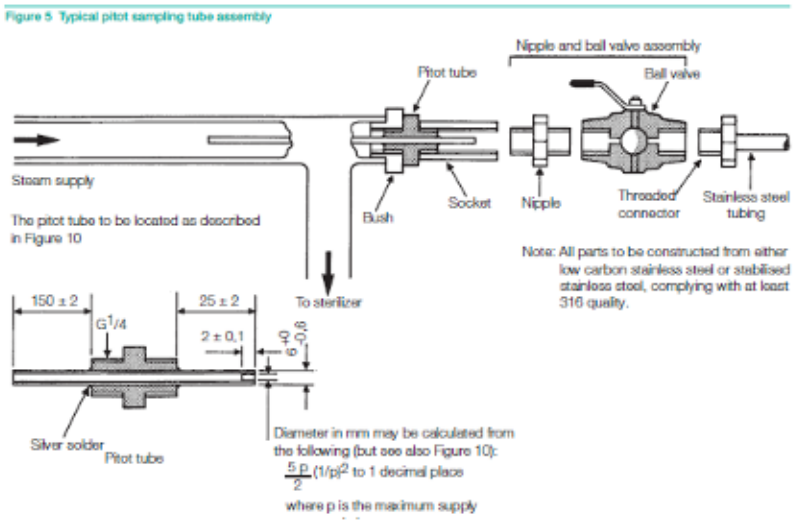
- **3.165** Figure 4 shows the apparatus connected to a pitot tube identical to the one specified for the steam quality tests in ‘Physical steam quality tests’. The pitot is fitted to the steam supply pipe near the sterilizer. This standard pitot is not suitable for laboratory samples.



Source: HTM-01-01 part C: Steam Sterilization (2016)

Steam sampling system for field analysis

- **3.165 …** Figure 5 shows an alternative pitot that may be used for all steam testing. If this pitot is used for field samples or the tests in paragraph 3.203, ‘Physical steam quality tests’, the ball valve, nipple and socket should be removed.

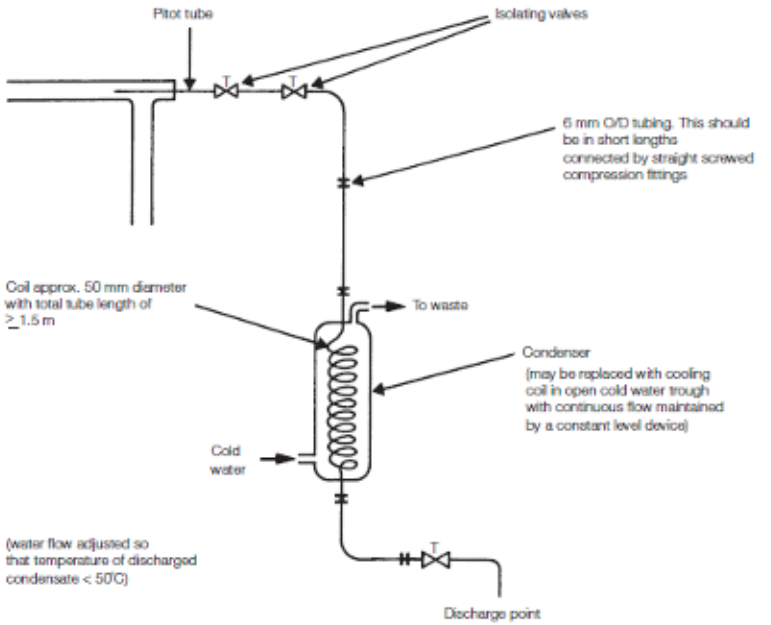


Source: HTM-01-01 part C: Steam Sterilization (2016)

Steam sampling system for laboratory analysis

- **3.175** This method is suitable for taking all required samples, including those to be subjected to full laboratory analysis and the test for pyrogens.
- All components, including the condenser and valves, are constructed in 316L stainless steel. The tubing is made in short sections connected by compression joints to form the required length and configuration. The sections are short enough to allow each element to be thoroughly cleaned, sterilized and depyrogenated before use.

Figure 6 Steam sampling system for laboratory analysis



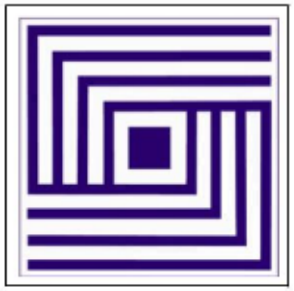
Note: The sampling circuit should be constructed from either low carbon stainless steel or stabilised stainless steel, complying with at least 316 quality.

Source: HTM-01-01 part C: Steam Sterilization (2016)

Critical parameters should be defined, monitored and recorded

STERIS
Life Sciences

Unused



Passing result

Incomplete air removal, Leak in autoclave

Non-condensable gas

Wet steam

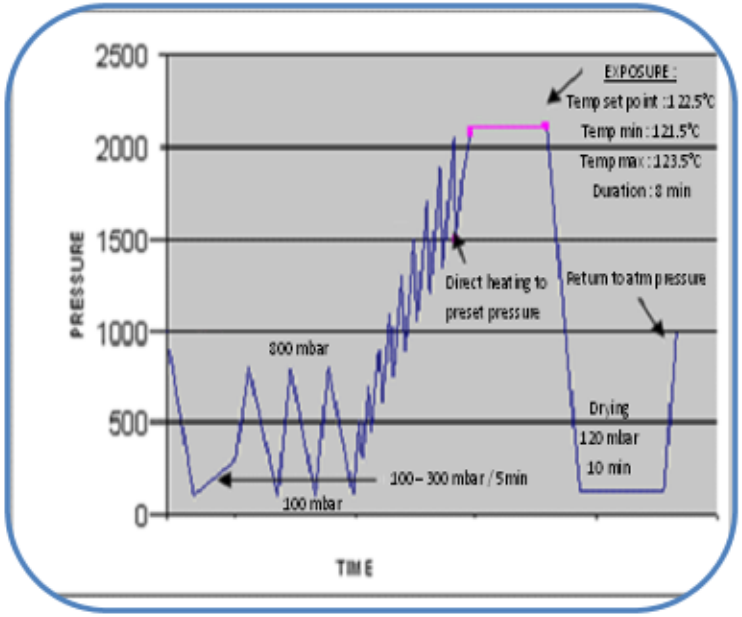
Superheated steam

These parameters should include consideration of the following examples: non-condensable gases, dryness value (dryness fraction), superheat and steam condensate quality.

Critical parameters should be defined, monitored and recorded

STERIS
Life Sciences

The quality of steam used for sterilization of porous loads and for Steam-In-Place (SIP) should be assessed periodically against validated parameters.



3 pre-vacuum
1.1 to 1.5 psia

Steam pulse
15.5 to 17 psia

Plateau
8 – 8.3 min

Post Vacuum for dry
1 min

Open autoclave

The validity of the process should be verified at scheduled intervals

STERIS
Life Sciences

Table 4 Periodic tests for porous-load sterilizers

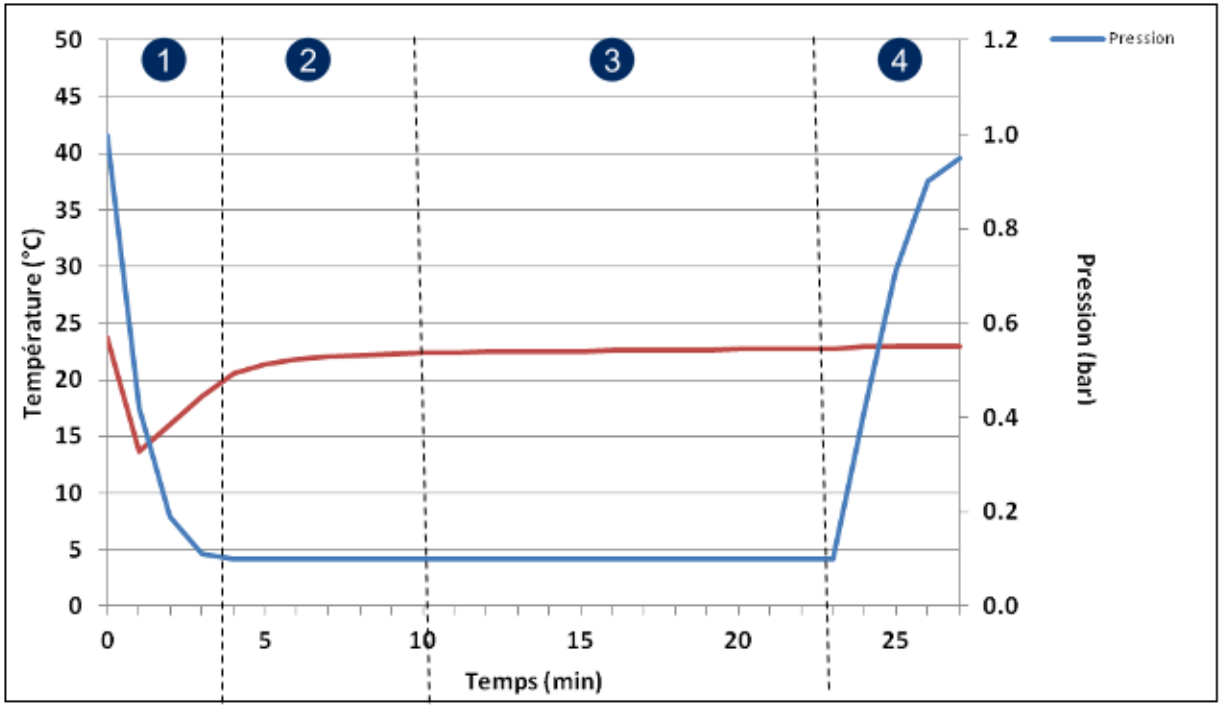
Daily test – User
Bowie-Dick test for steam penetration
Weekly tests – CP(D)
1. Weekly safety checks 2. Air leakage test 3. Air detector function test 4. Automatic control test 5. Bowie-Dick test for steam penetration*
Quarterly tests – CP(D)
1. Weekly safety checks 2. Air leakage test 3. Air leakage test (temperature and pressure sensors connected) 4. Automatic control test 5. Verification of calibration of sterilizer instruments* 6. Thermometric test for a small load* 7. Air leakage test (sensors removed) 8. Air detector function test 9. Bowie-Dick test for steam penetration
Yearly and revalidation tests – CP(D)
1. Yearly safety checks 2. Non-condensable gas test 3. Steam superheat test 4. Steam dryness test 5. Steam chemical purity tests 6. Air leakage test 7. Air leakage test (temperature and pressure sensors connected) 8. Automatic control test 9. Verification of calibration of sterilizer instruments* 10. Air detector performance test for a small load 11. Air detector performance test for a full load 12. Thermometric test for a small load 13. Thermometric test for a full load 13a. Load dryness test for a metal load (see BS EN 285) 14. Test for PRQ as required by the user 15. Air leakage test (sensors removed) 16. Air detector function test 17. Bowie-Dick test for steam penetration 18. Hollow load test
At a frequency defined by the manufacturer
1. Dynamic pressure test

* May be carried out simultaneously with the preceding test

Source: HTM-01-01 part C: Steam Sterilization (2016)

Critical parameters should be defined, monitored and recorded

When the sterilization process includes air purging (e.g. porous autoclave loads, lyophilizer chambers) there should be adequate assurance of air removal prior to and during sterilization. Loads to be sterilized should be designed to support effective air removal and be free draining to prevent the build-up of condensate.



1. Vacuum
2. Stabilization phase
3. Test phase -1.3 mbar/min
4. Increase in pressure

“BI results in isolation do not give assurance of sterilization and should not be used to override other critical parameters and process design elements.”

STERIS
Life Sciences

Description

	**Suspensions**	Liquid with spores that would be applied to a surface
	**Strips**	Rectangular paper with spores dried onto them that can be put into equipment or a device
	**Discs**	Circular paper, plastic or stainless steel with spores dried onto them that can be put into equipment or a device
	**Self Contained Biological Indicators (SCBIs)**	A combination of a disc or strip plus media inside a simple to use container
	**Process Challenge Devices (PCDs)**	A SCBI inside a larger device intended to be a worst case and repeatable package

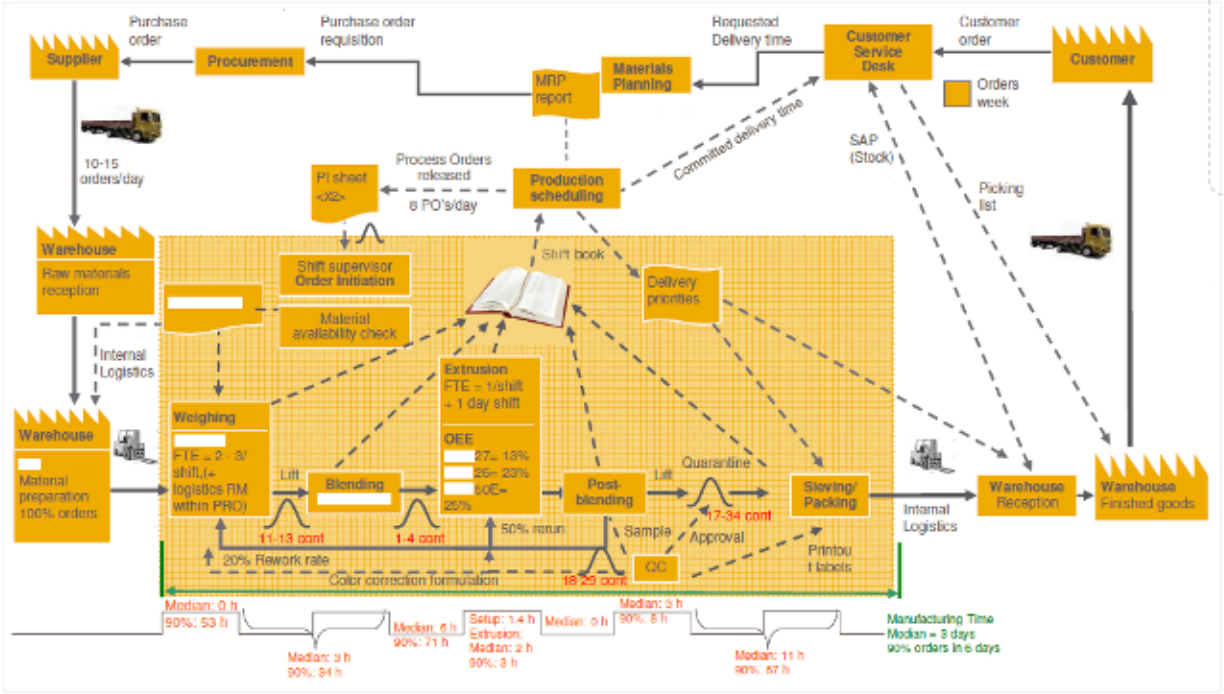
More Handling

Less Handling

The draft Annex 1 suggest that…

STERIS
Life Sciences

Prior to use of a new batch/lot of BI's, the quality of the batch/lot should be verified by conforming the viable spore count and identity



Quality

Compliance

FDA U.S. FOOD & DRUG ADMINISTRATION

"The reliability of vendor's Certificate of Analysis for batch/lots of BI's is established through an appropriate qualification program.
The frequency of testing prior to use of a new batch/lot of BIs should be based on the supplier QRM results.

Regulatory Requirements

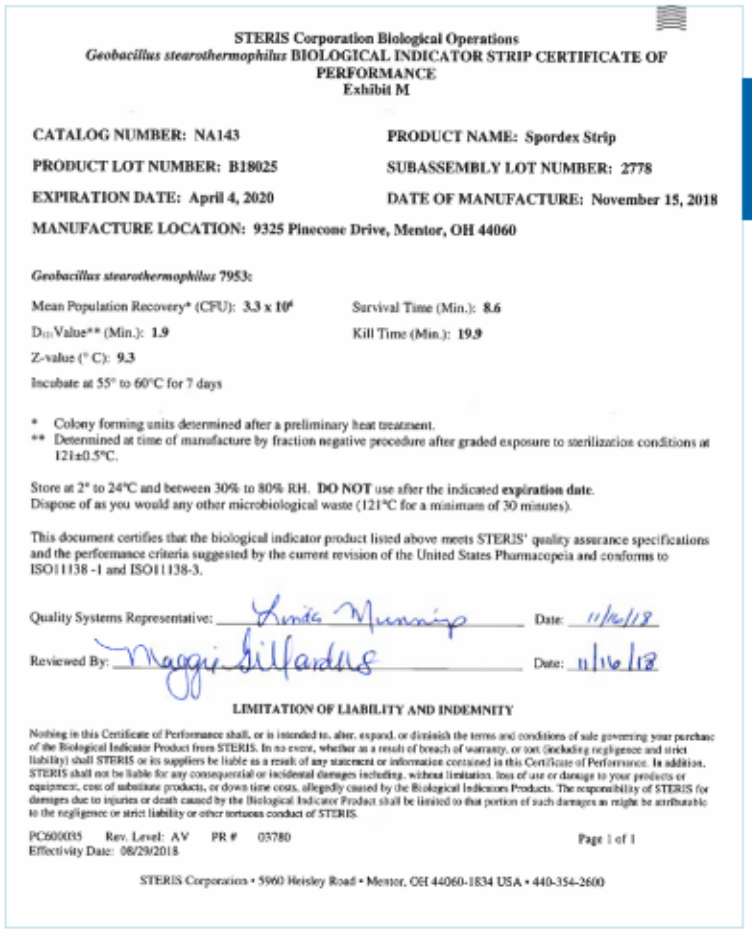
STERIS
Life Sciences

- BIs should be stored and used according to the manufacturer's instructions

- Where BIs are used to validate or monitor a sterilization process, positive controls should be tested for each sterilization cycle

- If biological indicators are used, strict precautions should be taken to avoid transferring microbial contamination to the manufacturing or other testing processes

Incoming Control of BI – Our Process



STERIS Corporation Biological Operations
***Geobacillus stearothermophilus* BIOLOGICAL INDICATOR STRIP CERTIFICATE OF PERFORMANCE**
Exhibit M

CATALOG NUMBER: NA143 **PRODUCT NAME: Spordex Strip**

PRODUCT LOT NUMBER: B18025 **SUBASSEMBLY LOT NUMBER: 2778**

EXPIRATION DATE: April 4, 2020 **DATE OF MANUFACTURE: November 15, 2018**

MANUFACTURE LOCATION: 9325 Pinecone Drive, Mentor, OH 44060

***Geobacillus stearothermophilus* 7953c**

Mean Population Recovery* (CFU): **3.3 x 10^6** Survival Time (Min.): **8.6**

D_{121}Value** (Min.): **1.9** Kill Time (Min.): **19.9**

Z-value (° C): **9.3**

Incubate at 55° to 60°C for 7 days

* Colony forming units determined after a preliminary heat treatment.
** Determined at time of manufacture by fraction negative procedure after graded exposure to sterilization conditions at 121±0.5°C.

Store at 2° to 24°C and between 30% to 80% RH. **DO NOT** use after the indicated **expiration date**.
Dispose of as you would any other microbiological waste (121°C for a minimum of 30 minutes).

This document certifies that the biological indicator product listed above meets STERIS' quality assurance specifications and the performance criteria suggested by the current revision of the United States Pharmacopeia and conforms to ISO11138 -1 and ISO11138-3.

Quality Systems Representative: Linda Munning Date: 11/16/18

Reviewed By: Maggie Gilfardus Date: 11/16/18

LIMITATION OF LIABILITY AND INDEMNITY

Nothing in this Certificate of Performance shall, or is intended to, alter, expand, or diminish the terms and conditions of sale governing your purchase of the Biological Indicator Product from STERIS. In no event, whether as a result of breach of warranty, or tort (including negligence and strict liability) shall STERIS or its suppliers be liable as a result of any statement or information contained in this Certificate of Performance. In addition, STERIS shall not be liable for any consequential or incidental damages including, without limitation, loss of use or damage to your products or equipment, cost of substitute products, or down time costs, allegedly caused by the Biological Indicators Products. The responsibility of STERIS for damages due to injuries or death caused by the Biological Indicator Product shall be limited to that portion of such damages as might be attributable to the negligence or strict liability or other tortuous conduct of STERIS.

PC600035 Rev. Level: AV PR # 03780 Page 1 of 1
Effectivity Date: 08/29/2018

STERIS Corporation • 5960 Heisley Road • Mentor, OH 44060-1834 USA • 440-354-2600

Upon arrival

- Check for any damages
- Store in a controlled refrigerator (temp – humidity)
- Check of the COA
  - Spore population
  - D-value
  - Survival and Kill time
  - External D-value determination for Apex

STERIS Life Sciences

Incoming Control of BI – Our Process

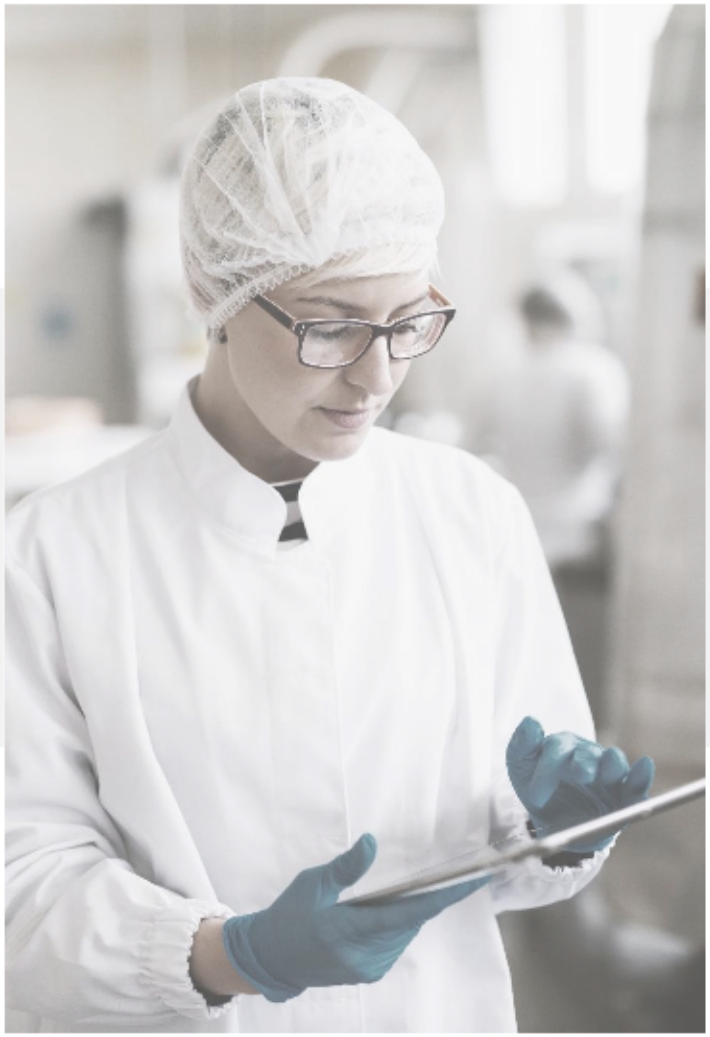
Example:
Storage/Control of SPORDEX

Temp: 2-24°C	Humidity: 30-80%
Spore count ≥ 10E6	D-value ≥ 1,5 min
Survival time ≥ 6min	Kill time ≥ 15 min

Incoming Control of BI – Our Process

Incoming control on every shipment of 4 BI

- Spore population
- Identification
- Purity
- Amp – colour check



Incoming Control of BI – Our Process

Example:
Population recovery of SPORDEX

- 4 BI
- 1 BI in test tube with 10ml AD and 5 glass beads
- Vortex and shake homogenous suspension
- Add 5ml AD
- 2 independent dilutions (1ml + 9ml AD)
- Heat shock + ice bath
- In duplo 1 ml of the suspension in PP + 50ml TSA
- Incubation for 48 hours at 55-60°C

Suitable protection after sterilization should be provided to prevent recontamination

STERIS
Life Sciences

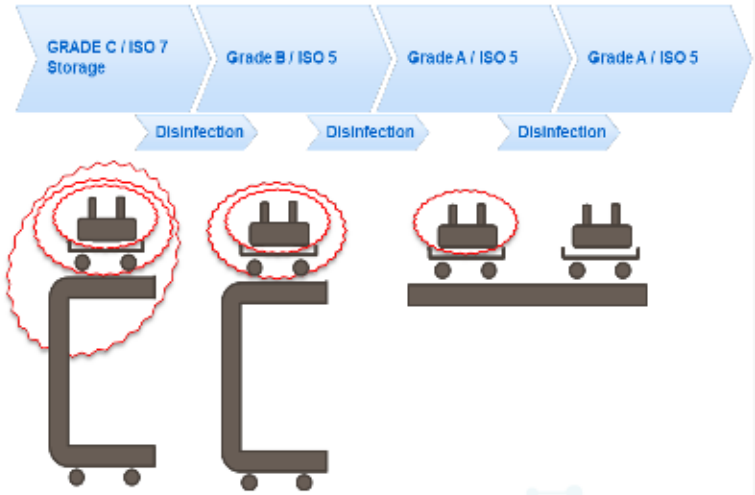
- Preparation of components and most products should be done in at least a grade D environment

- Where the product is at a high or unusual risk of microbial contamination then preparation should be carried out in a grade C environment.

- The unwrapping, assembly and preparation of sterilized equipment, components and ancillary items, the preparation and filling of product should all be treated as an aseptic process and performed in a grade A environment with a grade B background. Where an isolator is used the background should be in accordance with the grade

Number of layers would depends on the storage area and grade A continuity

If items **sterilized "in house" are not used immediately after sterilization, these should be stored, using appropriately sealed packaging, in at least a grade B environment**, a maximum hold period should also be established. Components that have been packaged with multiple sterile packaging layers need not be stored in grade B (where justified) if the integrity and configuration (e.g. multiple sterile coverings that can be removed at each transfer from lower to higher grade) of the sterile pack allows the items to be readily disinfected during transfer into the grade A zone.



Where materials, equipment, components and ancillary items are sterilized in sealed packaging or containers, the integrity of the sterile protective barrier should be qualified for the maximum hold time, and the process should include inspection of each sterile item prior to its use to ensure that the sterile protective measures have remained integral.

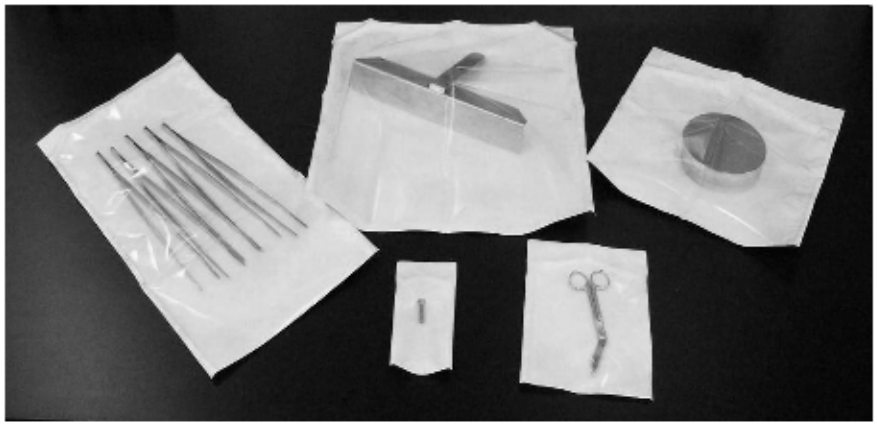
Agenda

1. Regulatory aspect and link
2. Sterilization and Moist Steam Quality vs draft Annex 1
3. Common mistakes observed
4. Conclusion and Q&A

Case study #1: Wet packs or loads : causes

STERIS
Life Sciences

- ✓ Pressure control
- ✓ Steam supply
- ✓ Condensation area
- ✓ Steam traps
- ✓ Autoclaves loads
- ✓ Packaging materials
- ✓ Dense load items are on top, resulting in condensation dripping on items below
- ✓ Autoclave jacket temperature
- ✓ Items touch the autoclave jackets
- ✓ Steam penetrates pouch and condenses on object, but is not removed during drying phase
- ✓ Drains



Case study #1: Minimize Amount of Condensation

PARAMETER	RANGE	DEFAULT
Number Of Pulses	1-99	3
First Pulse	Vacuum / Pressure	Vacuum
1st Vacuum Level	0.0-15.0 psia	1.5 psia
1st Vacuum Hold Time	0-600 s	0 s
1st Pressure Level	0.0-44.0 psia	21.5 psia
1st Pressure Hold Time	0-600 s	0 s
2nd Vacuum Level	0.0-15.0 psia	1.5 psia
2nd Vacuum Hold Time	0-600 s	0 s
2nd Pressure Level	0.0-44.0 psia	21.5 psia
2nd Pressure Hold Time	0-600 s	0 s
3rd Vacuum Level	0.0-15.0 psia	1.5 psia
3rd Vacuum Hold Time	0-600 s	0 s
3rd Pressure Level	0.0-44.0 psia	21.5 psia
3rd Pressure Hold Time	0-600 s	0 s

Post Sterilization Cycle Conditioning:

- ✓ Quick evacuation (vacuum) of steam: vacuum levels and hold times are adjustable program input parameters
- ✓ Utilize pulse / heated drying
- ✓ Extend drying time: Less condensation during prevacuum, heat up and sterilization allows for shorter drying time
- ✓ Increase drying temperature
- ✓ Increase cooling time

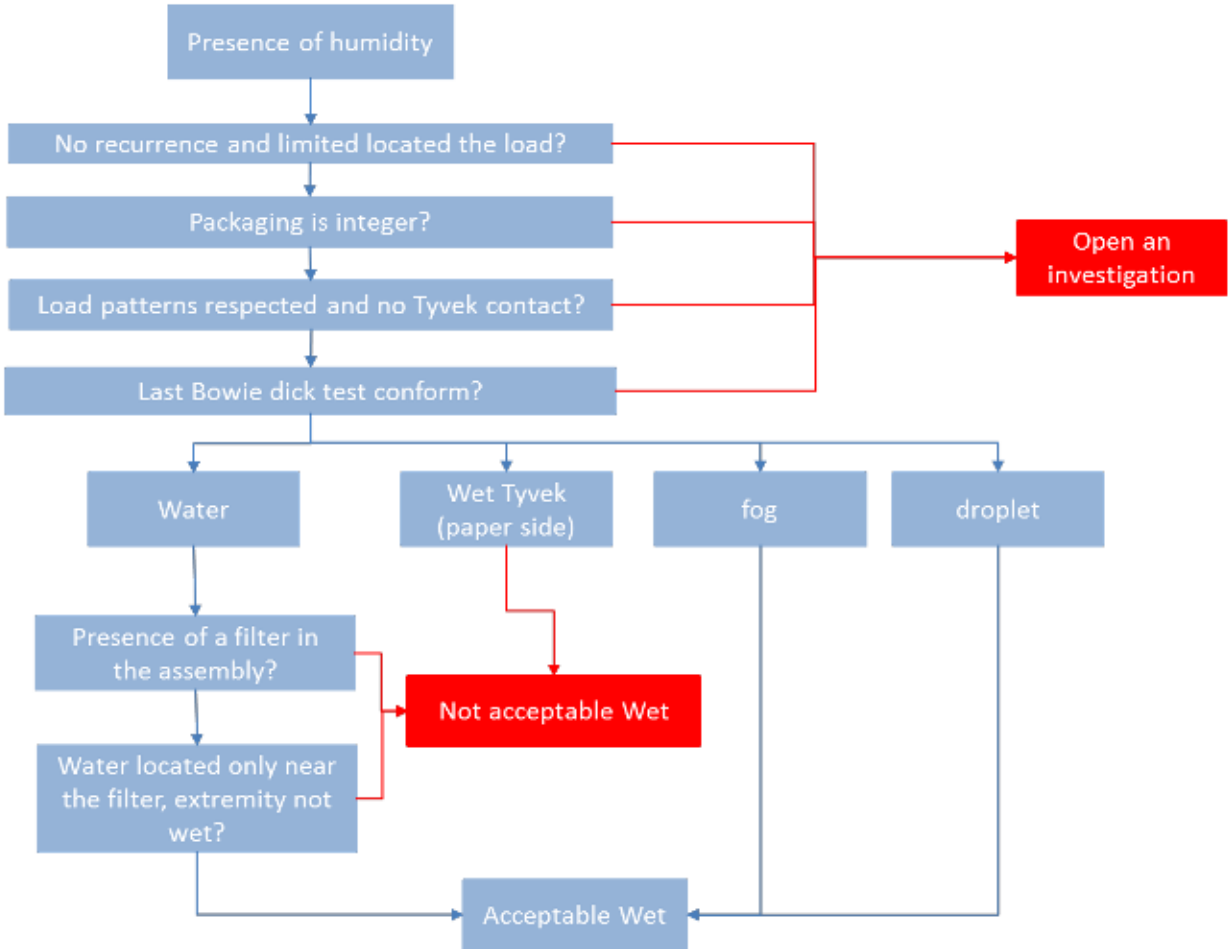
Wrapping management;

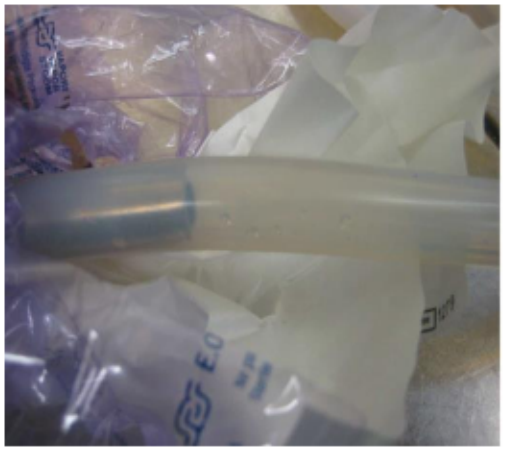
- ✓ Items vertically positioning
- ✓ Leave sufficient space between wrapped items
- ✓ Tyvek | Tyvek

Case study #1: Wet packs: Is it acceptable ?

- ✓ Wet packs or wet loads equal risk for sterility assurance
- ✓ Some instance can be acceptable if correctly justified – for e.g. filter wet with WFI prior autoclave. but, too much water in the set after sterilization and drying cycle is non acceptable

Decisional tree for presence of wet packs or items:

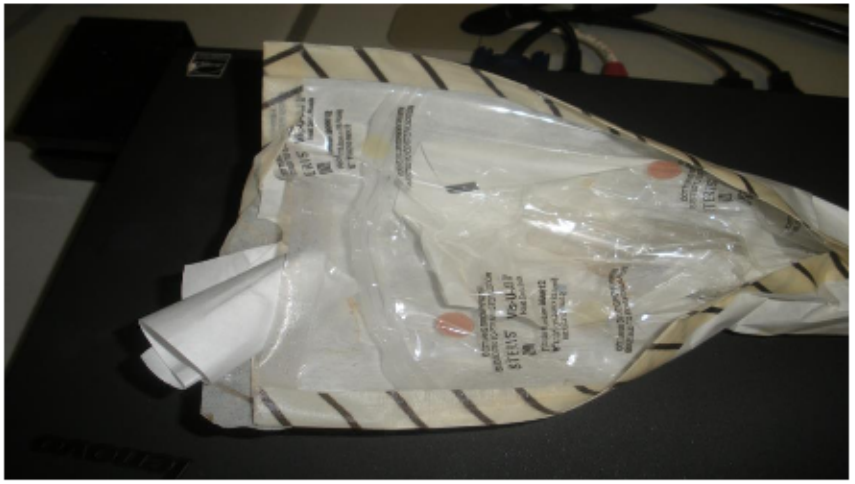




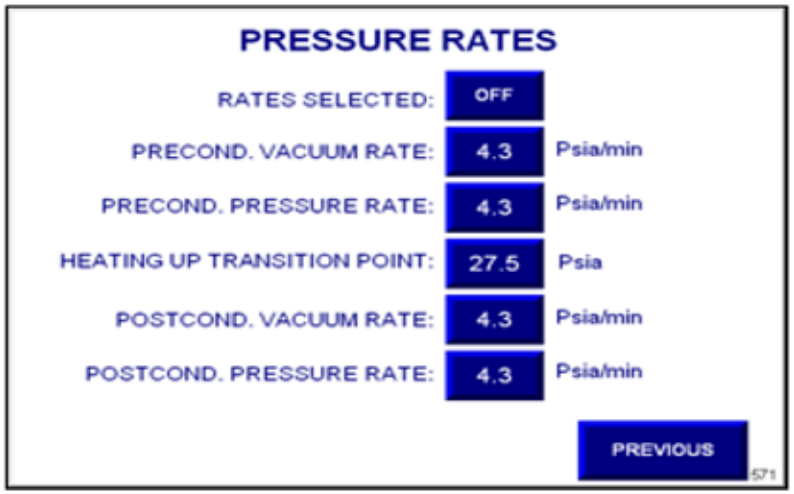
Case study #2: Burst Autoclave Bags : Doubled bagged product that burst, why if bags are designed for prevacuum?

STERIS
Life Sciences

- ✓ Manufacturing Defect
- ✓ Improperly sized bags/wrapping
- ✓ Too many layers of bags
- ✓ Pressure change (vacuum and/or steam injection) too quick (pre-vac, heat-up, post)



Case study #2: Burst Autoclave Bags : Solution



Utilize a rate function to control the pressure/vacuum operation in the sterilizer.

- ✓ Change vacuum / pressure rate during prevacuum pulses
- ✓ Change vacuum / pressure rate during sterilization post conditioning

Wrapping management:

- ✓ Wrapping not too tight and not too large

Case study #3: Steam contact

STERIS
Life Sciences

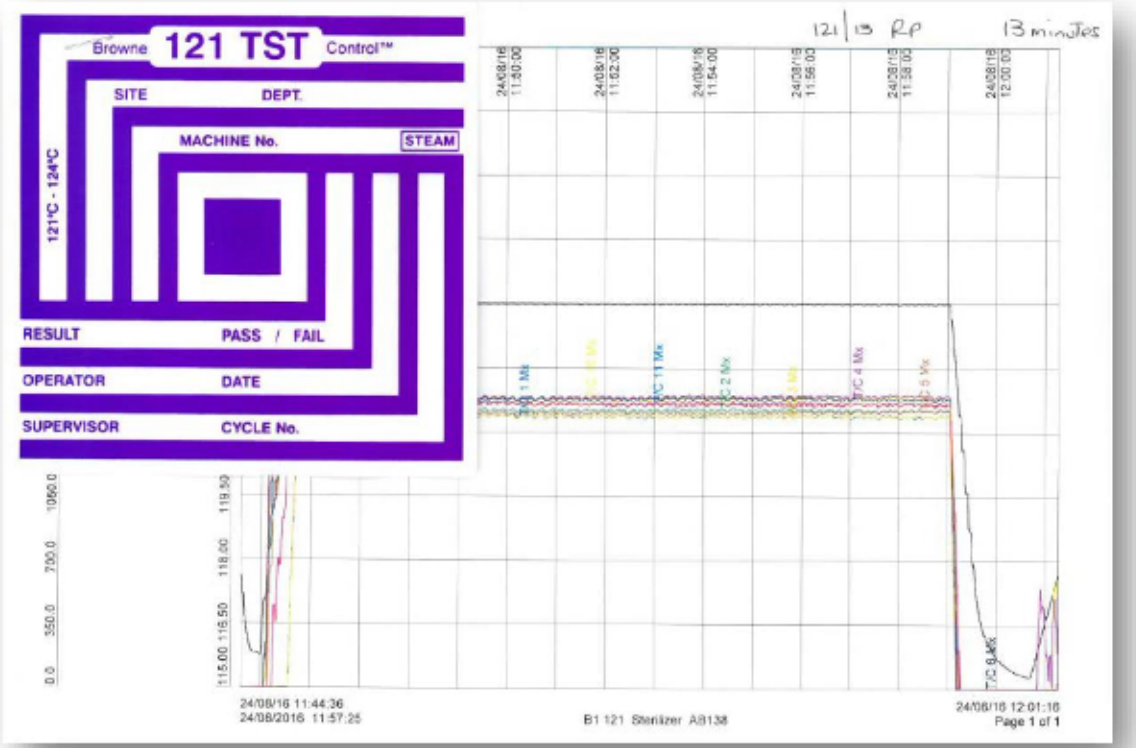
Potential problem areas:

- ✓ Closed Valves / tightened screw caps or secured aluminum foil
- ✓ Tied waste bags
- ✓ Areas enclosed in a load packed too tightly.

Solutions:

- ✓ Ensure valves are open and inspect loads for spots that are completely enclosed.
- ✓ Do not packs loads too tight
- ✓ Leave bags open at least some to allow air to escape and steam to penetrate (decontamination cycle)

Case study #4: Longer time Bowie Dick exposure lead to false positive



Case study #5: Bowie Dick test showing improper autoclave performance

STERIS
Life Sciences

Case study #6: Inadequate storage of a Bowie Dick test will show false negative

STERIS
Life Sciences

Case study #7: Residue Remaining on Parts

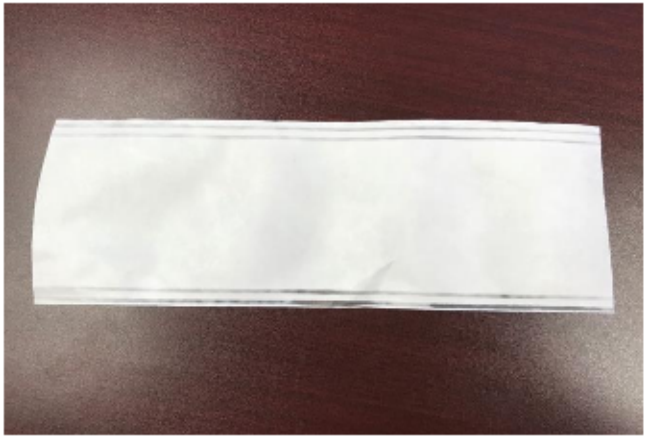
STERIS
Life Sciences

Possible Cause:

- Condensation pooling onto stainless steel through Tyvek bowl cover, wet cover contacting equipment, drying, leaving residue spot

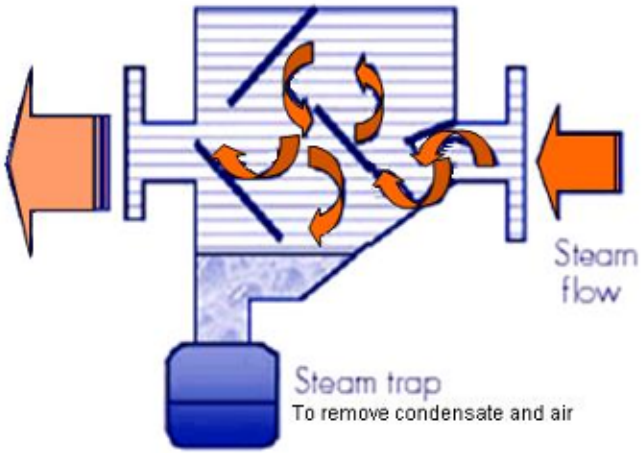
Possible Solution:

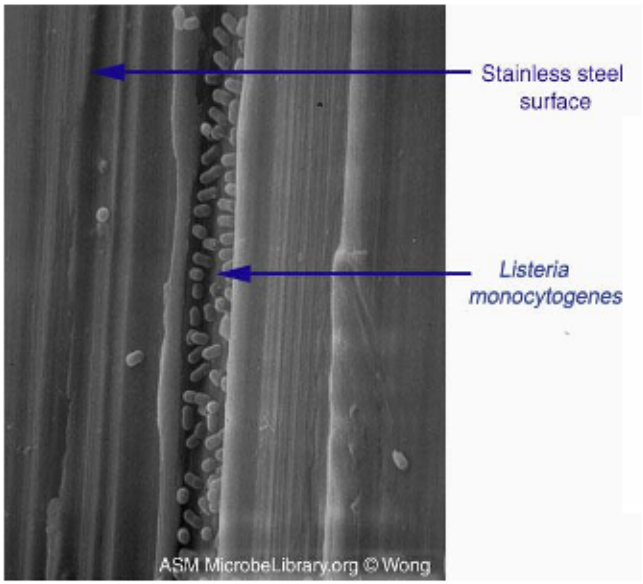
- Modify equipment position in autoclave to present condensation from pooling
- Add slip sheet between Tyvek and stainless steel



Case study #10: For Steam-In-Place systems, it may also be necessary to record the temperature at condensate drain locations throughout the sterilization period.

STERIS
Life Sciences





If a biofilm becomes established, these bacteria can leach into the product

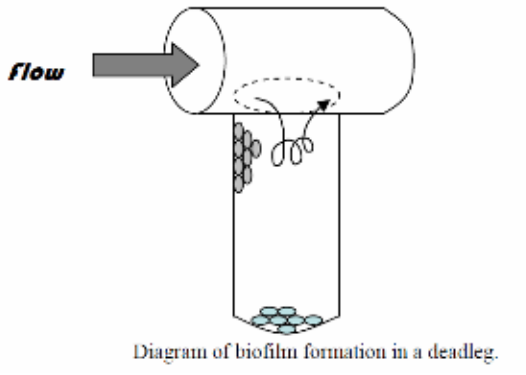


Diagram of biofilm formation in a deadleg.

The system should be appropriately designed and validated to assure all parts of the system are subjected to the required treatment.

Case study #11: Do not stick the BI or put the BI in an envelop prior SIP validation

STERIS
Life Sciences

Spore Trap

Tea infuser

SIP is easy to automate and validate using thermocouples and biological indicators

SIP involves the use of specific components such as steam traps, pressure regulators and sterilizing vent filters to evacuate air and condensate, and maintain the sterility of the equipment following sterilization.

Challenge between Production, Qualification group & QC lab

Good Communication!

- Approved BI's available
- Incubation between 4 hours after the end of the sterilization cycle
- Availability of equipment in production
- Determination of the worst case positions in the equipment
  - Logical
  - Temperature study
  - Chemical colour indicators

Conclusion

STERIS
Life Sciences

- ✓ Inspections:
  - ✓ specific topics (e.g. Bis, BDs, etc..) are not deep dive
  - ✓ Sterility assurance level and microbial contamination is a focus
- ✓ MRA between the USA and EU may suggest to be in compliance with the FDA aseptic guideline is enough expect in some cases e.g. vaccine, cell therapy, etc
- ✓ The aim of the sterility assurance level strategy is to define the ethos of a site's approach to sterility control from preparation to use of the sterile product
- ✓ The biggest challenges for Annex 1 implementation is the execution of risk management and incorporating risk culture into organizations

Thank You

For your listening

El Azab Walid
Technical Service Manager – STERIS
Walid_elazab@steris.com
+32479790273

References

Note: This is not a complete listing, just a guidance to literature the speaker has found to be interesting/beneficial.

- ✓ Draft EMA Guideline on the sterilization of the medicinal product, active substance, excipient and primary container
- ✓ Annex 1 EU GMP
- ✓ PDA TR 1 (2007): Validation of moist heat sterilization processes: cycle design, development, qualification and ongoing control
- ✓ PDA TR 48 (2010): Moist heat sterilizer systems: Design, commissioning, operation, qualification and maintenance
- ✓ Practical Guide to Autoclave Validation, *Pharmaceutical Engineering* Jul 2002
- ✓ Autoclave testing in a university setting, *Applied Biosafety* 10(4):248-252. 2005
- ✓ Validation study and routine control monitoring of moist heat sterilization procedures. *Biocontrol Science* 17(2):57-67. 2012
- ✓ EN 285, Sterilization – Steam Sterilizers – Large Sterilizers, CEN European Committee for Standardisation (1996)

STERIS
Life Sciences

BI – From Reception to Analysis

Reception and Analysis:

- Verify the transport document validation
- Verify CoA
- Store in appropriate environment
- Test population:
  - Heat chock:
  - 10' B.A. at 80°C- 85°C
  - 10-15' GTS at 95°C -100°C
- Test D-Value:
  - Performed on 20-25 samples depending on the process gradient
  - Maintain the temperature : 121 +/-5°C
  - Perform the test for time of the D value refer in the CoA

Specific Recommendation - BI Use (2/5)

BI Storage

Follow Supplier Instruction for storage

- Temperature
  - B. atropheaus
  - G. Stearothermophilus
- Relative Humidity
  - Will depend on the BI – 30 -80%
- Dark and Light
  - Preferably in the Dark
- Surrounding environment (chemicals)
- Shelf-life

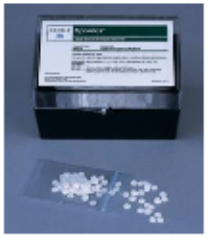
BI – From Reception to Analysis

STERIS Life Sciences

Use

- Send aseptically to the site
- Manipulated aseptically the Biological indicators
- Start the cycle
- End of the cycle
  - Aseptic manipulation is a Key!
  - Collect the BI
  - Send it to the QC within a validated time : < 4h
- Reception at the QC:
  - Quick reception and storage is key
  - Quick testing and incubation is better
  - Follow the supplier methods

BI – From Reception to Analysis (4/5)



Reception and Incubation

Reception at the QC:

- Control the process time and temperature
- Quick reception and storage is key
- Identify correctly the reference BI
- Aseptic manipulation is key
- Quick testing and incubation is better
- Follow the supplier methods

Specific Recommendation - BI Use

BI culture

- Type of media
  - Media – conventional BI's
  - Media included - SCBI
- Aseptic handling
- Positive/negative controls
- Use the supplier methods

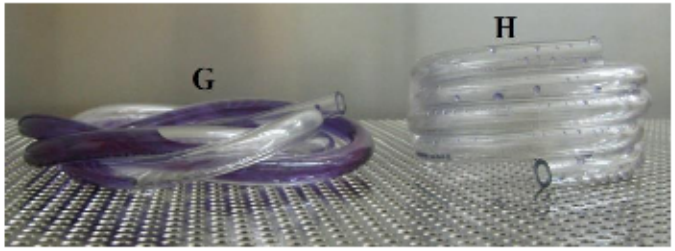
BI Incubation

- Incubation time and temperature
  - G. stearothermophilus – 7 days at 55 – 60°C
  - B. atrophaeus – 7 days at 30 – 35°C
- Check growth
- Reduce Incubation Time (RIT)
  - Require validation prior to use the method
  - Require pre-approval by your notified body (medical device)
  - Follow FDA 510(k) guidance for BI manufacturers (medical device)
- Use the supplier methods

Factors Involved in Producing a Sterile Product

STERIS
Life Sciences

Typical Steam Sterilization Cycles



- ✓ **Gravity cycle**
  - Can be used for items such as unwrapped metal components, glassware, or non-porous items **that do not entrap air.**

- ✓ **Pre-Vacuum Cycle**
  - Can be used for porous or double wrapped goods, tubing, glassware that cannot be inverted or placed on its side.

- ✓ **Liquid Cycle**
  - Should be used for liquids in vented borosilicate glass

Top consideration when validating an autoclave

STERIS
Life Sciences

Top Consideration

1. Sterilization cycle
2. Load configuration
3. Worst case load and location
4. Choosing the right control for liquid
5. Thermocouple wire
6. Acceptance criteria
7. Thermocouple accuracy verification
8. Document the validation test runs
9. SOP and Training tools
10. Project planning
11. Control and on-going monitoring

Parameters to understand and control

The number and the intensity of the prevacuum may differ depending:

a. Hard goods vacuum – ex.: open glassware, piping, etc....

b. Wrapped goods vacuum – hoses, vent filter, vessels, empty bottles, etc…

c. Liquids vacuum

The design of the cycle/programme used for sterilization should be decided using QRM principles

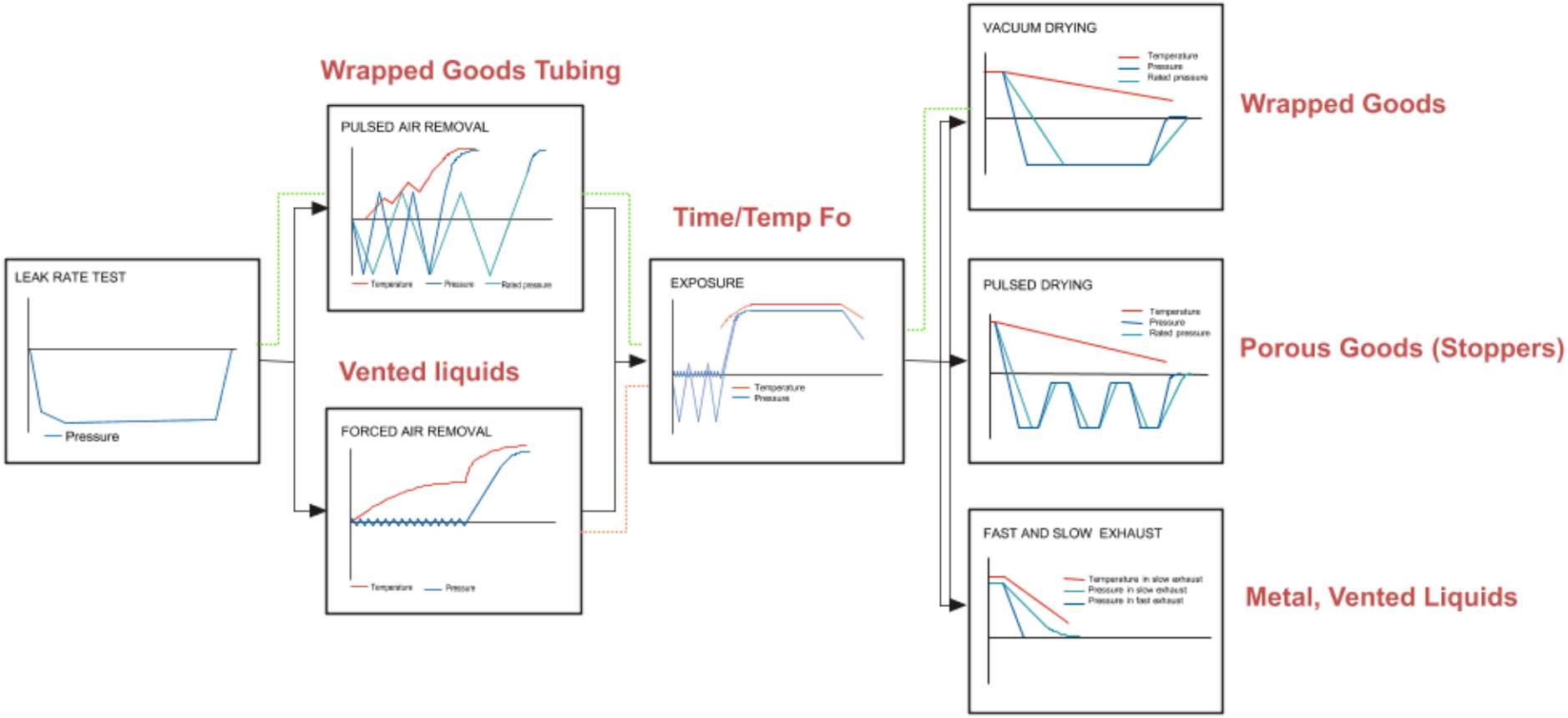
STERIS
Life Sciences

Pre-Cycle

Pre-Conditioning

Exposure

Post-Conditioning



Top consideration when validating an autoclave

STERIS
Life Sciences

Top Consideration

1. Sterilization cycle
2. Load configuration
3. Worst case load and location
4. Choosing the right control for liquid
5. Thermocouple wire
6. Acceptance criteria
7. Thermocouple accuracy verification
8. Document the validation test runs
9. SOP and Training tools
10. Project planning
11. Control and on-going monitoring

Parameters to understand and control

Different type of load configuration can be validated:

a. Fix load

b. Fix/variable load

c. Variable load

Top consideration when validating an autoclave

STERIS
Life Sciences

Top Consideration

1. Sterilization cycle
2. Load configuration
3. Worst case load and location
4. Choosing the right control for liquid
5. Thermocouple wire
6. Acceptance criteria
7. Thermocouple accuracy verification
8. Document the validation test runs
9. SOP and Training tools
10. Project planning
11. Control and on-going monitoring

Parameters to understand and control

Determine which load configuration are the worst case and the worst case location within the items:

a. Location in the load and in the item:
   - ✓ Center
   - ✓ Volume, length, etc..

b. Temperature with the load and ite
   - ✓ Wrapping method
   - ✓ Center – "in the deep"
     - ✓ Cut
     - ✓ Insert the thermocouple
     - ✓ seal the slot

"be careful, it is important to never affect the ability of the items to be sterilized"

Top consideration when validating an autoclave

STERIS
Life Sciences

Top Consideration

1. Sterilization cycle
2. Load configuration
3. Worst case load and location
4. Choosing the right control for liquid
5. Thermocouple wire
6. Acceptance criteria
7. Thermocouple accuracy verification
8. Document the validation test runs
9. SOP and Training tools
10. Project planning
11. Control and on-going monitoring

Parameters to understand and control

More than one control could be validated.
Different parameter to be took in account:

a. Size of the bottle and its fill volume

b. Thickness of the glass

c. Viscosity of the liquid

"The liquid Control will ideally be the one that is the most difficult to sterilize (worst-case) and will be located at the coldest spot in the chamber "

Top consideration when validating an autoclave

STERIS
Life Sciences

Top Consideration

1. Sterilization cycle
2. Load configuration
3. Worst case load and location
4. Choosing the right control for liquid
5. Thermocouple wire
6. Acceptance criteria
7. Thermocouple accuracy verification
8. Document the validation test runs
9. SOP and Training tools
10. Project planning
11. Control and on-going monitoring

Parameters to understand and control

Acceptance criteria should be set prior protocol approval:

a. Porous cycles :
   - ✓ min. SAL 10^{-6}

b. Liquid cycles:
   - ✓ min. SAL 10^{-6}
   - ✓ F_0> 15 at the end of the cycle

c. Range 3°C: 121.1°C -1°C/+2°C

d. Dry load visually

e. All BI are negative and control positive

Top consideration when validating an autoclave

STERIS
Life Sciences

Top Consideration

1. Sterilization cycle
2. Load configuration
3. Worst case load and location
4. Choosing the right control for liquid
5. Thermocouple wire
6. Acceptance criteria
7. Thermocouple accuracy verification
8. Document the validation test runs
9. SOP and Training tools
10. Project planning
11. Control and on-going monitoring

Parameters to understand and control

Some consideration when using wired thermocouple:

a. Leakage of the wire: risk of failed leak test.

b. Difficult to place into the item without adversely affecting the item's ability to be sterilised

c. Difficult to place wires inside sealed bottles without:
   i. touching the inside wall
   ii. Compromising the bottle's ability to be sterilized

Top consideration when validating an autoclave

STERIS
Life Sciences

Top Consideration

1. Sterilization cycle
2. Load configuration
3. Worst case load and location
4. Choosing the right control for liquid
5. Thermocouple wire
6. Acceptance criteria
7. Thermocouple accuracy verification
8. Document the validation test runs
9. SOP and Training tools
10. Project planning
11. Control and on-going monitoring

Parameters to understand and control

cPQ

PQ

Specifications

URS

OQ

DQ & FAT

IQ

Implementation

Legend:
- **Use of SAP products**
- **No use of SAP products**