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Filter Integrity Test fault handling - GMP view

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Contents:

- GMP requirements
- Pre and Post Use Integrity Testing
- Impact of new EU GMP Annex 1 requirements
- Fault handling
- Closed Container Integrity Testing

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Sterile filtration

- Can be used to sterilise gases or liquids
  - Typically the product itself, disinfectants and service gases
- Removes microorganisms from the gas or liquid being filtered
- Sterilising grade filter is 0.22 µm
- To work:
  - Filter and its housing must be sterile
  - Pipework and equipment after the filter must be sterile
- Other grades of filter can be used to reduce the bioburden
  - But not sterilise




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Sterile filtration testing

- Need to test that:
  - Product is not affected by being filtered
  - Filter does sterilise
    - 107cfu/ cm2 *Brevundimonas diminuta*
  - Filter is integral (no “holes”) and has a perfect seal in its housing




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Sterile filtration testing

- FDA requirements
  - FDA: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice Guidance for Industry SEPTEMBER 2004 (IX B)
  - Things to consider as part of filtration validation and normal use ….

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Sterile filtration testing

- *"Factors that can affect filter performance generally include*
  - *Viscosity and surface tension of the material to be filtered*
  - *pH*
  - *Compatibility of the material or formulation components with the filter itself*
  - *Pressures*
  - *Flow rates*
  - *Maximum use time*
  - *Temperature*
  - *Osmolality*
  - *The effects of hydraulic shock"*

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Sterile filtration testing

- *"When designing the validation protocol, it is important to address the effect of the extremes of processing factors on the filter capability to produce sterile effluent. Filter validation should be conducted using the worst-case conditions, such as maximum filter use time and pressure"*

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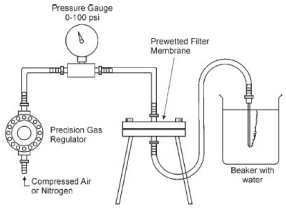
Sterile filter integrity testing

- In the past a "bubble point" test was used
  - Filter is wetted
  - Air pressure allied on dirty side
  - Air pressure slowly increases
  - Looking for the point at which the surface tension of the liquid in the filter breaks
  - Resulting in a large release of bubble from the clean side



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Sterile filter integrity testing

- Now automated equipment is used – a pressure hold test
  - Test equipment supplied by filter manufacture
- This was done after you have used the filter

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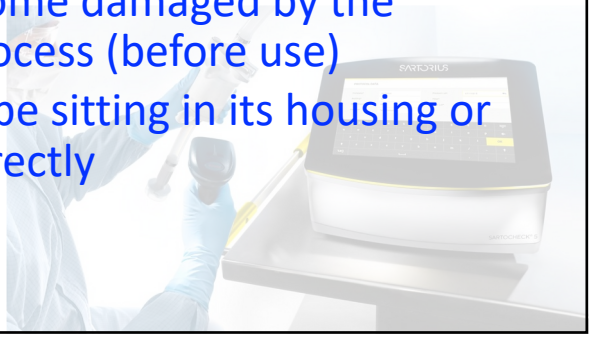
Sterile filter integrity testing PUPSIT

- Background:
  - Filter may have a hole in it that is plugged as part of the filtration process
  - May then pass a post-use integrity test, but batch is not sterile
  - Filter may become damaged by the sterilisation process (before use)
  - Filter may not be sitting in its housing or connected correctly



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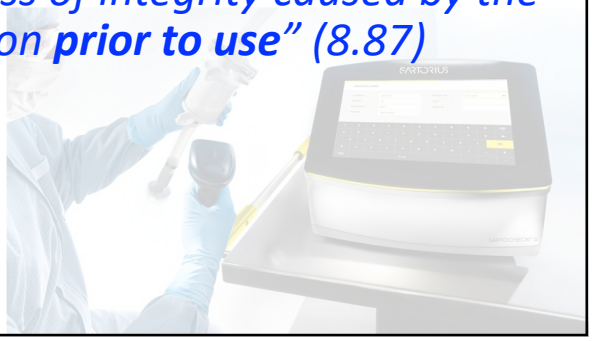
Sterile filter integrity testing PUPSIT

- New Annex 1:
  - *"The integrity of the sterilised filter assembly should be verified by integrity testing before use (pre-use post sterilisation integrity test or PUPSIT), to check for damage and loss of integrity caused by the filter preparation **prior to use**" (8.87)*



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Sterile filter integrity testing PUPSIT

- Issues:
  - To Integrity Test a filter it needs to be wet
    - Immediate problem for gas filters as these will then need to be dried
  - You need to have the ability to Integrity Test the filter in its housing in-situ
    - Often the filter and housing are Integrity Tested by disconnecting them after use and taking them to a Integrity Test location

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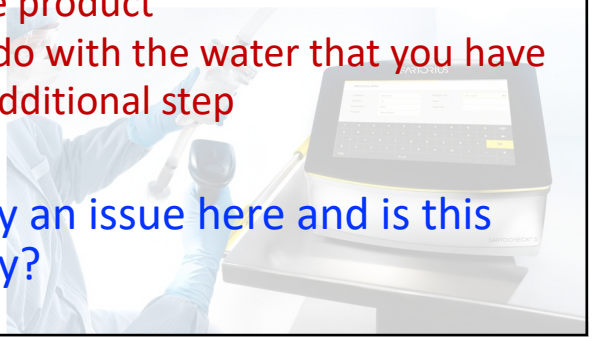
Sterile filter integrity testing PUPSIT

- Issues:
  - Option to wet the filter – **product**
    - Loss of product as part of the wetting process
  - Option to wet the filter – **water**
    - An additional step
    - Dilution of the product
    - What do you do with the water that you have filtered – an additional step
  - Is there actually an issue here and is this really necessary?



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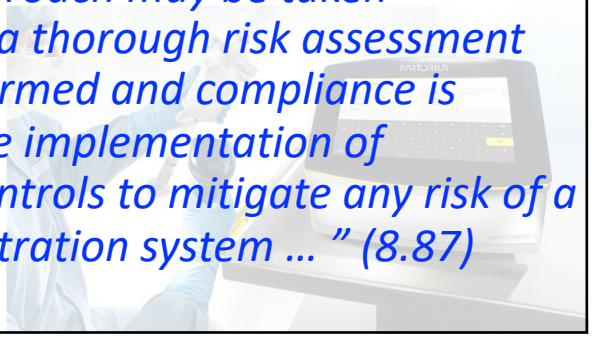
Sterile filter integrity testing PUPSIT

- New Annex 1 (continued):
  - *"It is recognized that PUPSIT may not always be possible after sterilisation due to process constraints (e.g. the filtration of very small volumes of solution). In these cases, an alternative approach may be taken providing that a thorough risk assessment has been performed and compliance is achieved by the implementation of appropriate controls to mitigate any risk of a non-integral filtration system … " (8.87)*



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Sterile filter integrity testing PUPSIT

- Question: Any challenges that you have with PUPSIT in your facility?

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Any questions?

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Fault handling

- It is possible to make an integrity test result invalid
- Typical examples:
  - Integrity test equipment fails
  - Correct pressures not achieved
  - Test not set-up correctly
  - Operator error

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Fault handling

- There needs to be a formal system to investigate such failures
  - Similar approach to dealing with Out Of Specification results in the laboratory
- Failures need to be recorded in the batch record
  - Along with any supplier certificates and print-outs

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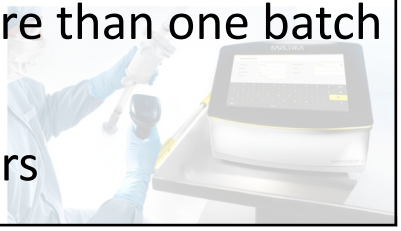
Fault handling

- In the event of a true failure then the equipment and (unless enclosed) the area, need to be viewed as contaminated
  - Re-cleaned, sanitised and sterilised as necessary
- Consideration needs to be given to other products and other batches, especially if the filter is in use for more than one batch
- Failures of gas/ vent filters



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Any questions?

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Closed Container Integrity Testing

- Single-used closed systems that need to be sterile will be sterilised by the manufacturer (irradiation)
  - Need to have certification for this
- It is critical that the unit is integral and has no leaks
- Needs to be pressure tested with sterile air before use
  - Pressure test equipment supplied by manufacturer

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References

- EU GMP Directives and Guidelines:
- https://ec.europa.eu/health/documents/eudralex/vol-4_en

- FDA: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice Guidance for Industry SEPTEMBER 2004
- https://www.fda.gov/regulatory-information/search-fda-guidance-documents/sterile-drug-products-produced-aseptic-processing-current-good-manufacturing-practice

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