Filtration and CCIT

Contents:

- Filter Integrity Testing
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Current Annex 1 requirements (110 - 115):

- *"Filtration alone is not considered sufficient when sterilisation in the final container is possible. With regard to methods currently available, steam sterilisation is to be preferred. If the product cannot be sterilised in the final container, solutions or liquids can be filtered through a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties, into a previously sterilised container. Such filters can remove most bacteria and moulds, but not all viruses or mycoplasmas. Consideration should be given to complementing the filtration process with some degree of heat treatment."*

Current Annex 1 requirements (110 - 115):

- You must sterilise the product by Terminal Sterilisation in its final contain if this is possible
- Steam is preferred
- You can use sterile filtration:
    - 0.22 micron filter (min)
    - Into sterile containers
    - Some heat treatment can also be applied
- Filters do not remove all viruses and mycoplasmas

Current Annex 1 requirements (110 - 115):

- *Due to the potential additional risks of the filtration method as compared with other sterilization processes, a second filtration via a further sterilised micro-organism retaining filter, immediately prior to filling, may be advisable. The final sterile filtration should be carried out as close as possible to the filling point.*
  - A second filter is advised (in case first filter fails)
  - Final filter should be as close to the point of filling as possible

- *Fibre-shedding characteristics of filters should be minimal.*
  - Need to show that the filter does not introduce fibres into the product

Current Annex 1 requirements (110 - 115):

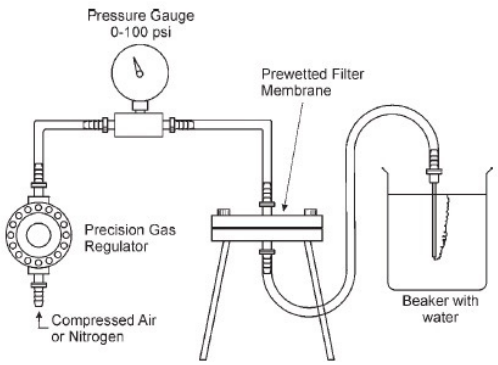
- *The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as a bubble point, diffusive flow or pressure hold test. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter should be determined during validation and any significant differences from this during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record. The integrity of critical gas and air vent filters should be confirmed after use. The integrity of other filters should be confirmed at appropriate intervals.*

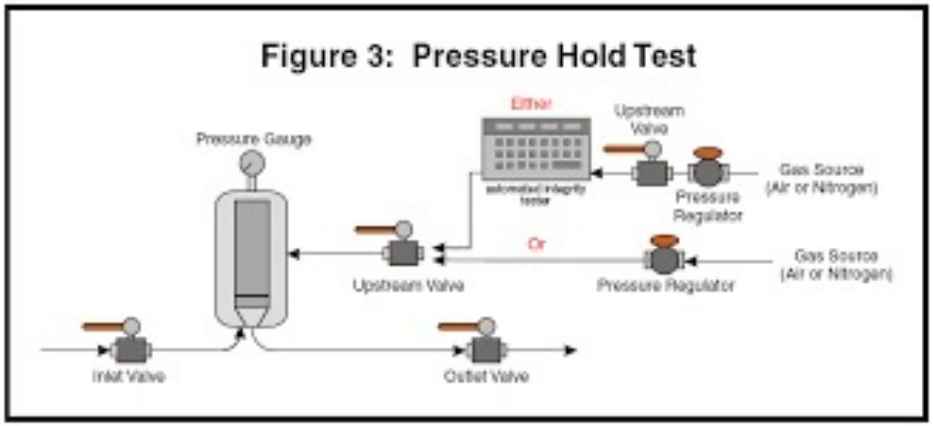
Current Annex 1 requirements (110 - 115):

- Need to know that the filter works by integrity testing it
- This needs to be done in-situ
- Can be done manually (bubble point) or using equipment
- Verified before use – can integrity test or use suppliers certificate
- Confirmed after use – need to integrity test
- Filters used over a longer period of time (such as gas or vent filters) need to be integrity tested too

Current Annex 1 requirements (110 - 115):

- *The same filter should not be used for more than one working day unless such use has been validated.*
  - This is for product or media filtration filters
  - Concern is to do with “grow through” of microorganisms
- *The filter should not affect the product by removal of ingredients from it or by release of substances into it.*
  - Need to validate the filter to show that it does not affect the product



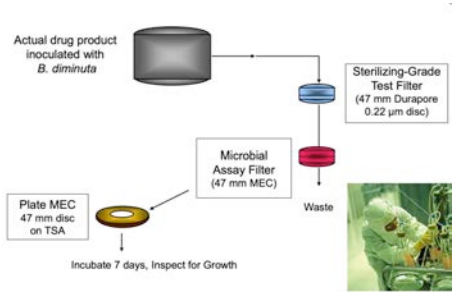


FDA requirements:

- FDA: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice Guidance for Industry SEPTEMBER 2004 (IX B)

- *Validation should include **microbiological challenges** to simulate **worst-case production conditions** for the material to be filtered and integrity test results of the filters used for the study.*
- ***Product bioburden** should be evaluated when selecting a suitable challenge microorganism to assess which microorganism represents the **worst-case challenge to the filter**.*
- *The microorganism **Brevundimonas diminuta** (ATCC 19146) when properly grown, harvested and used, is a common challenge microorganism for 0.2 µm rated filters because of its small size (0.3 µm mean diameter).*

  – Additional guidance on the validation of the filter using microorganisms



FDA requirements:

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- *Factors that can **affect filter performance** generally include*
- *(1) **viscosity** and surface tension of the material to be filtered*
- *(2) **pH**, (3) **compatibility** of the material or formulation components **with the filter itself***
- *(4) **pressures**, (5) **flow rates**, (6) maximum use **time***
- *(7) **temperature**, (8) **osmolality**, (9) and the effects of **hydraulic shock**.*

- *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.*

  – Things to consider as part of filtration validation and normal use

FDA requirements:

- FDA: Sterile Drug Products Produced by Aseptic Processing — Current Good Manufacturing Practice Guidance for Industry SEPTEMBER 2004 (IX B)

- ***Integrity testing*** *of the filter(s)* ***can be performed prior to processing****, and should be routinely* ***performed post-use****.*
- *It is important that integrity testing be conducted after filtration to detect any filter leaks or perforations that might have occurred during the filtration.*
- ***Forward flow*** *and* ***bubble point tests****, when appropriately employed, are two integrity tests that can be used.*
- *A production filter's integrity test specification should be consistent with data generated during bacterial retention validation studies.*

  - A suggestion to integrity test before use where possible
  - Must integrity test afterwards
  - Integrity test needs to be consistent with any validation studies

Integrity test failure

- Little guidance given
- A failure is a failure and the results must be acted on accordingly
- If the test can be **invalidated** then it can be repeated
  - For example if the test was **not set up or performed correctly**
  - Can only invalidate **if the incorrect test can be shown not to have affected the filter and its status**

Closed Container Integrity Testing

- Can the integrity of a unit be tested before and after use?

- Might be able to do a pressure decay test
- May need to get assurances from the supplier

- Both of the above

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