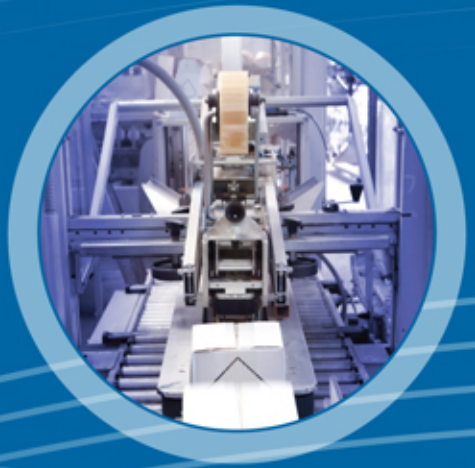
Connecting People, Science and Regulation

STERILE FILTRATION: Clarification Proposal Annex 1 Paragraph 113: Focus on Pre-use/Post-sterilization Integrity Testing



Hemisha Ly (Merck)
on behalf of PDA
PUPSIT Taskforce

Issue

Paragraph 113:

The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as bubble point, diffusive flow or pressure hold.

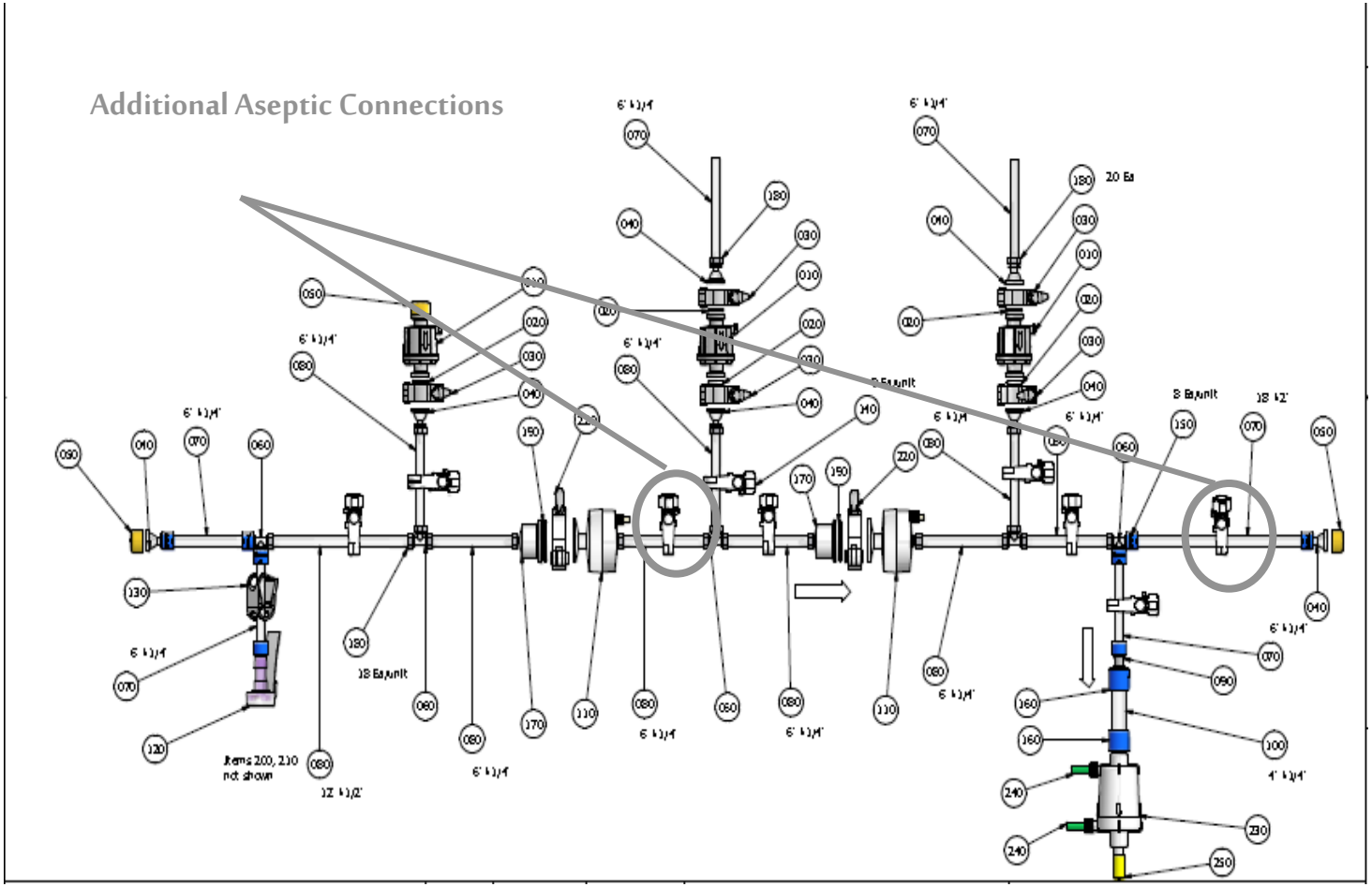
What is not new

- Annex 1 had the debated wording of paragraph 113 included for a long time, without being enforced.
- Filters can be damaged during steam sterilization, especially when the process is improperly validated; however, the damage is dramatic and detectable during post-use testing.
- The damage sufficient to compromise the filter integrity has not been demonstrated to be undetectable by the integrity testing.

What is new

- Some European inspectors started enforcing the debated paragraph 113, others did not
  - Enforcement created a multitude of different down-stream designs and increase in complexity
  - Risk analysis showed risk elevation, due to complexity and down-stream manipulations, when using pre-use/post-sterilization integrity testing
- Current Q&A (posted in 2007) causes confusion
  - Mixed practiced by European Inspectors - cases where risk-based approach is accepted and other where this was not accepted

Design Complexity Example



Additional Components

2 Vent Filters

1 Hydrophobic Filter

1 Hydrophilic Filter

3 Sanitary Connects

2 2-way valves

Bottled WFI

Compressed Air

courtesy of Roche Genentech

Concerns

- There is a risk (which has been demonstrated) that integrity testing, manipulations etc. resulting from post-sterilization/pre-use integrity testing can introduce downstream contamination.
  - PDA Journal of Pharmaceutical Science and Technology, Vol. 66, No. 5, September–October 2012, *Pre-use/Post-sterilization Integrity Testing of Sterilizing Grade Filters,* PDA Pre Use/Post-Sterilization Integrity Test Task Force.

Category	w/ Test	w/o Test	Rational
Severity	4	4	If the filter fails or microbial ingress happens, it has a major effect in both cases
Frequency	3	2	Microbial ingress into the downstream side has occurred, for this reason the downstream side is commonly held under pressure after steam sterilization. This overpressure is replaced by atmospheric pressure during the pre-use test (3). Since steam sterilized downstream processes are commonly held at overpressure the likelihood of ingress is lower (2).
Detectability	3	1	If there is a microbial ingress due to downstream manipulation, when the test is performed, it will not be detected (3). If the filter is flawed due to the steam sterilization process it will be readily detected by the post-use test (1).
Risk level	36	8	Risk assessment would not recommend a pre-use/post-sterilization test.

- There may be a risk (which has never been demonstrated) that a non-integral filter before use can become integral by the time of post-use testing.
  - No published scientific journal or article have been found

Reaction & Activities

PDA contacted by multiple drug manufacturers for clarification & comment

Tasks assigned:

- gain meeting appointment w/ EMA
- creation of clarifying presentation for the meeting

PDA-EMA Meeting to discuss and clarify the topic (May 5th 2011, London)

Tasks assigned:

- submittal of revised Q&A to replace 2007 Q&A
- proposal to align inspectors

Reaction & Activities

Task Force Formation
(leader: Hemisha Ly, Merck & Co.)

Tasks assigned:

- abbreviation of the formerly submitted Q&A
- assembly of interested companies
- creation of PDA Position Paper
- presentation for a November 15th 2011 meeting

Tasks Completed

- PDA Position Paper– approval from PDA Advisory Boards & Board of Directors
- Published PDA's Recommendation in PDA Journal Sep/Oct 2012 Issue
- Discussion at PIC/S Workshop, May 9th & 10th, Geneva

Current Status – PDA Initiatives

- Continue to work with EMA to replace the 2007 Q&A with new Q&A that allows for risk-assessments to be utilized to justify whether or not post-sterilization pre-use testing is needed

  - Current Q&A causes confusion

    - Mixed practiced by European Inspectors - cases where risk-based approach is accepted and other where this was not accepted

  - Reference to the correct paragraph – change from “Paragraph 85” to “Paragraph 113”

- PDA has offered to train Inspectors/Investigators on this subject

Proposal

Post-Sterilization/pre-use integrity testing of a sterilized filter would mean manipulation of the sterilized filtrate side. PDA & Industry sees this as a process risk elevation.

PDA's Recommendation:

Since the risk in performing a pre-use/post-sterilization integrity test depends upon the application and design of the process, the need of a pre-use integrity test of a sterilized filter should be left to the discretion by the filter user and shall not be mandatory.

Q&A on Integrity Testing

What are the main causes of integrity test failures?

- Majority of integrity test failures are due to incomplete wetting of the filter membrane structure.
- Other, rarer, causes are damage created during handling, during in-line steam sterilization, or by exposure to excessive differential pressures during filtration.

Q&A on Integrity Testing

Can flawed filters be detected by the post-use integrity test?

- Flaws of the filter would be detected pre- as well as post-use.
- There is no evidence that a filter which was not integral after sterilization would not be detected after use.

Q&A on Integrity Testing

What is the likelihood of detecting a post sterilization integrity failure during post filtration integrity testing?

- There is no evidence that a filter which was not integral after sterilization would not be detected after use.
- Moreover, a properly qualified and executed filter sterilization process diminishes the risk of damaging a filter during sterilization.

Q&A on Integrity Testing

Does a pre-use/post sterilization integrity test require the sterilized filtrate side manipulation?

- The filter membrane requires wetting before an integrity test is performed.
- Therefore, the downstream side will be subjected to an aseptic manipulation to remove the wetting fluid and to dry the filter.
- Even where no downstream manipulation is required, there remains a risk (however small) of contamination just by conducting the test

Q&A on Integrity Testing

Are there benefits to performing a pre-use/post sterilization integrity test?

- Yes, a damaged filter would be found and possible batch rejection is avoided.
- However, the benefit is an economical one, not a drug safety issue, as the damaged filter would also be detected during the post-use test.
- A pre-use/post sterilization test may be associated with a higher risk, due to filtrate side manipulation.

Q&A on Integrity Testing

Is it possible to design a filtrate process, which allows pre-use/post sterilization integrity testing?

- Such designs are possible and require specific downstream equipment for venting and collection of wetting fluid.
- However, the extended downstream design would introduce more process complexity and increase risk of processing mistakes.
- Risk analysis of a filtration system with and without a pre-use is recommended. Specific system design, validation and operator training should be considered to mitigate the potential risks associated with the downstream equipment.

Q&A on Integrity Testing

How can the risk of sterilization damage be mitigated?

- By qualifying the sterilization process and determine the appropriate, process related parameters.
- By designing systems to control and monitor process parameters such as recommended pressure and/or temperature limits to assure that they are not exceeded.

Q&A on Integrity Testing

In what instances would it be possible not to pre-use integrity test the sterilizing grade filter and rely on the post-use integrity test to demonstrate that the filter has remained integral throughout usage?

- When it has been demonstrated using a thorough risk-based analysis, which includes all reasonable scenarios for implementation, that the likely risk of contamination would increase if post-sterilization integrity testing is implemented.
- As part of the risk-based approach, a control strategy should be implemented, including validation and in-process monitoring of the sterilization process to ensure that the vendor recommended parameters have not been exceeded.

FINAL TAKE-AWAYS

- PDA PUPSIT Task Force recommends: The EMA Q&A from 2007 should be replaced to allow for an option to use a risk-based approach
- There is strong need to align the Inspectors and minimize confusion
  - Cases where European Inspectors accepted a risk-based approach and cases where it was not accepted
- The decision to perform or not perform a post-sterilization/pre-use integrity test should be made by the filter user upon thorough, documented risk-based analysis in accordance with ICH guidelines.
  - Enforcement has caused complex processes and procedures to be established