Regulatory Trends in Manufacturing of Sterile Medicinal Products by Filtration

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Presentation Scope

Common vocabulary

Current sterile medicinal product regulations & guidances

Future regulatory direction for sterile medicinal products
Scope
– Sterile Medicinal Products
Aseptically produced
Sterile Medicinal Products Produced by Aseptic Processing

Uses multiple sterilization processes designed for individual components
Sterile Core Focus
Formulation / Filling Suite – Filtration Highlights
Common Vocabulary
What Does “Should” Mean

**US FDA**


"The use of the word should in Agency guidances means that something is suggested or recommended, but not required"

**PICS**

RECOMMENDATION ON THE VALIDATION OF ASEPTIC PROCESSES, PI 007-6, January 2011

"the term "should" indicates requirements that are expected to apply unless shown to be inapplicable or replaced by an alternative demonstrated to provide at least an equivalent level of quality"
“Aseptic filling: Operation whereby the product is sterilised separately, then filled and packaged using sterilised containers and closures in critical processing zones.”

“Bioburden: Total number of viable microorganisms on or in pharmaceutical product prior to sterilisation.”

“Integrity test: Test to determine the functional performance of a filter system.”

“Sterile: Free of any viable organisms. (In practice, no such absolute statement regarding the absence of microorganisms can be proven, see sterilisation.)”

“Sterilisation: Validated process used to render a product free of viable organisms.”
Some Useful Filtration Definitions

Sterilising Filter - “a sterile filter of nominal pore size of 0.22 micron (or less), or with at least equivalent micro-organism retaining properties” (PICS PE-009 GMP Guide)
“A sterilizing grade filter should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent” (FDA)
“A filter that reproducibly removes all test microorganisms from the process stream, producing a sterile effluent.” (PDA TR26)

Serial Filtration - Filtration through two or more filters of the same or decreasing pore size one after the other (PDA TR26)

Redundant filtration - A type of serial filtration where a second sterilizing filter is used as a backup in the event of an integrity failure of the primary sterilizing filter. (PDA TR26)
Traditional style sterile filtration system with bioburden reduction filter and EMA compliant

Use a second microorganism retentive filter as close as possible to the filling point
Traditional style sterile filtration system with bioburden reduction filter and EMA compliant, and FDA compliant for “at risk” product (redundant final filtration system) at POU

Use a sterilizing filter and a second sterilizing filter as close as possible to the final use
Redundant Filtration
Filtration is a common method of sterilizing drug product solutions. A sterilizing grade filter should be validated to reproducibly remove viable microorganisms from the process stream, producing a sterile effluent. Currently, such filters usually have a rated pore size of 0.2 \( \mu m \) or smaller. Use of redundant sterilizing filters should be considered in many cases.

The manufacturing process controls should be designed to minimize the bioburden of the unfiltered product.

Bioburden of unsterilized bulk solutions should be determined to trend the characteristics of potentially contaminating organisms.
111. Due to the potential additional risks of the filtration method as compared with other sterilisation 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.”
What is Redundant Filtration?

Serial Filtration
Filtration through two or more filters of the same or decreasing pore size, one after the other.

Redundant Filtration
A type of serial filtration in which a second sterilizing-grade filter is used as a backup in the event of an integrity failure of the primary sterilizing filter.

Key point for a redundant filtration is that each filter alone is capable of delivering a sterile filtrate and that at least one of them is integral at the end of the process
In the event an additional sterilizing-grade filter is placed in the filter train to ensure against the loss of product due to potential failure of the primary sterilizing filter, the additional filter does not require post-use integrity testing unless the primary sterilizing filter fails.

In that case, the second, or redundant filter, must satisfactorily pass post-use integrity testing. (Note: The primary sterilizing filter in the filter train should be the last filter in the series).

For processes requiring in-series integrity testing (e.g., where both filters are sterilized in series), each filter must be tested individually. Precautions should be taken to maintain the sterility of the fluid pathway between the two filters.
Pupsit

Pre-use
Post-sterilization Integrity Testing
Annex 1 to Volume 4 of EU GMP
(only for countries in Europe)

“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 a bubble point, diffusive flow or pressure hold” test.

2017 PICS guidelines
(for PICS member countries OR countries who export to PICS members)

“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 a bubble point, diffusive flow or pressure hold test.”
Some Reasons for PUPSIT

Comments from EMA in 2011 - Q&A on GMP
“The filter sterilisation process, may be physically stressful for the filter. For example high temperatures during the process may cause the filter to distort, potentially leading to fluid pathways that allow the passage of particles greater than 0.2μm in size. The performance of a filter can improve with use, as particles begin to block individual pathways and remove larger pathways that smaller particles could successfully navigate. For these reasons filters should be tested both before use but after sterilisation, and again after use.”

Economic batch disposition
If the filter fails post-use FIT then the batch is discarded or reprocessed (if practicable)

Other considerations that can affect pre-use filter integrity
Mechanical damage to filter (shipping / handling etc.), filter housing maintenance (issues with damage to surface or code 7 base in housing), etc.
Three Major PUPSIT Misconceptions in mid 2017

**PUPSIT has not been required until now**
Response: PUPSIT has been in the EMA regulations and PICS guidelines since 1997 (or 2007 according to one EMA inspector)

**PUPSIT was going to be removed from the regulations**
Response: Guidelines are regularly revised. PUPSIT was not one of the items that EMA was going to change

**Customers have no choice and MUST do PUPSIT**
Response: Customers can either perform PUPSIT or provide a written risk assessment document to show that the risk of doing PUPSIT is greater than the current risk of not doing PUPSIT
Common regulatory Threads and Direction in 2016 & 2018
Example of Revised EMA / PICS Documentation
Guideline on process validation for finished products – Nov 2016
- information and data to be provided in regulatory submissions

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# Example of Revised EMA / PICS Documentation

## Guideline on manufacture of the finished dosage form – Jan 2018

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Regulations, Guidances - Current & Future
Draft Regulations – Revision of Annex 1 of EU GMP Guide
Guidelines to Good Manufacturing Practice for Medicinal Products
– manufacture of sterile medicinal products

“The revised Annex 1 has been prepared in co-operation with the EMA, World Health Organization (WHO), and PIC/S in order to maintain global alignment of standards, and provide assurance of product quality.”

Major step in aligning EMA / PICS with WHO
First major revision of Annex 1 in 10 years
Current Annex 1 is 16 pages long. Draft Annex 1 revision is 50 pages long
Example of Additional Recommendations in Draft Annex 1 Revision

8.15 Aseptic manipulations (including non-intrinsic aseptic connections) should be minimized using engineering solutions such as the use of preassembled and sterilized equipment. Whenever feasible, product contact piping and equipment should be pre-assembled, then cleaned and sterilized in place. The final sterile filtration should be carried out as close as possible to the filling point and downstream of aseptic connections wherever possible.
Example of Additional Specific Recommendations in Draft Annex 1 Revision – detail missing from Current Annex 1
Filtration of medicinal products which cannot be sterilized in their final container

8.78 If a liquid product cannot be terminally sterilized by a microbiocidal process, it should be sterilized by filtration through a sterile, sterilizing grade filter (with nominal pore size of 0.22 micron (or less) or with at least equivalent micro-organism retaining properties), and subsequently aseptically filled into a previously sterilized container, the selection of the filter used should ensure that it is compatible with the product, see 8.119.

Suitable bioburden reduction and/or sterilizing grade filters may be used at multiple points during the manufacturing process to ensure a low and controlled bioburden of the liquid prior to the primary sterilizing grade filter.

Due to the potential additional risks of a sterilizing filtration process as compared to other sterilization processes, a second filtration through a sterile, sterilising grade filter (positioned as per clause 8.15), immediately prior to filling, is advisable
Example of Additional Specific Recommendations in Draft Annex 1 Revision – detail missing from Current Annex 1
Filtration of medicinal products which cannot be sterilized in their final container

8.79 The selection of components for the filtration system (including air, gas and vent filters) and their interconnection and arrangement within the filtration system, including pre-filters, should be based on the critical quality attributes of the products, documented and justified.

The filtration system should not generate fibres, unacceptable levels of impurities or otherwise alter the quality and efficacy of the product. Similarly, the filter characteristics should not be adversely affected by the product to be filtered.

Adsorption of product components and extraction/leaching of filter components should be evaluated
Example of Additional Specific Recommendations in Draft Annex 1 Revision – detail missing from Current Annex 1
Filtration of medicinal products which cannot be sterilized in their final container

8.80 The filtration system should be designed to:

a) Allow operation within validated process parameters.
b) Maintain the sterility of the filtrate.
c) Minimise the number of aseptic connections required between the sterilizing filter and the final filling of the product.
d) Allow cleaning procedures to be conducted as necessary.
e) Allow sterilization procedures, including SIP, to be conducted as necessary. The sterilization procedures should be validated to ensure achievement of a target sterilization assurance level (SAL) of 10^-6 or better (e.g. 10^-7).
f) Permit in-place integrity testing, preferably as a closed system, prior to filtration as necessary. In-place integrity testing methods should be selected to avoid any adverse impact on the quality of the product.
Example of Additional Specific Recommendations in Draft Annex 1 Revision – detail missing from Current Annex 1
Filtration of medicinal products which cannot be sterilized in their final container

8.81 Liquid-sterilizing filtration should be validated during initial process validation. Validation can be grouped by different strengths or variations of a product, but should be done under worst-case conditions. The rational for grouping fluids should be justified and documented.

8.82 Wherever possible, the product to be filtered should be used for bacterial retention testing. Where the product to be filtered is not suitable for use in bacterial retention testing, a suitable surrogate product should be justified for use in the test. The challenge organism used in the bacterial retention test should be justified.
Example of Additional Specific Recommendations in Draft Annex 1 Revision – detail missing from Current Annex 1

Filtration of medicinal products which cannot be sterilized in their final container

8.83 Filtration parameters that should be considered in validation and routine processing should include but are not limited to:

a) If the system is flushed or integrity tested in-situ with a fluid other than the product, then flushing with the product should be part of the process.

b) The wetting fluid used for filter integrity testing based on filter manufacturer’s recommendation or the fluid to be filtered. For the latter, the appropriate integrity test value specification should be established.
Example of Additional Specific Recommendations in Draft Annex 1 Revision – detail missing from Current Annex 1
Filtration of medicinal products which cannot be sterilized in their final container

8.83

c) Filtration process conditions including:

i. Fluid prefiltration holding time and effect on bioburden.

ii. Filter conditioning, with fluid if necessary.

iii. Maximum filtration time/total time filter is in contact with fluid.

iv. Flow rate.

v. Filtration volume.

vi. Temperature.

vii. The time taken to filter a known volume of bulk solution and the pressure difference to be used across the filter. Any significant differences from those validated to those observed during routine manufacturing should be noted and investigated. Results of these checks should be included in the batch record.
Examples of Key Differences in Draft Annex 1 Revision
- Filter Integrity Testing

Filtration of medicinal products which cannot be sterilized in their final container

8.84 The integrity of the sterilized filter assembly should be verified by testing before use, in case of damage and loss of integrity caused by processing, and should be verified by on line testing immediately after use by an appropriate method such as a bubble point, diffusive flow, water intrusion or pressure hold test.

It is recognised that for small batch sizes, this may not be possible; in these cases an alternative approach may be taken as long as a formal risk assessment has been performed and compliance is achieved.

There should be written integrity test methods, including acceptance criteria, and failure investigation procedures and justified conditions under which the filter integrity test can be repeated.

Results of the integrity tests (including failed and repeated tests) should be included in the batch record.
8.87 Where serial filtration (one filtration is followed by a subsequent filtration) is a process requirement the filter train is considered to be a sterilizing unit and all sterilizing-grade filters within it should satisfactorily pass integrity testing both before use, in case of damage during processing, and after use.

8.88 Where a redundant sterilizing filter is used, the additional filter does not require post-integrity testing unless the primary sterilizing filter fails, in which case the redundant filter must then satisfactorily pass post-use integrity testing. Bioburden samples should be taken prior to the first filter and the sterilizing filter, systems for taking samples should be designed so as not to introduce contamination.

8.89 Liquid sterilizing filters should be discarded after the processing of a single lot. The same filter should not be used for more than one working day unless such use has been validated.
8.119 The compatibility of materials used for product contact surfaces with the products should be ensured under the process conditions by evaluating e.g. adsorption and reactivity to the product.

8.120 Extractable profile data obtained from the supplier of the components of SUS may be useful to ensure that extractables and leachables from the SUS do not alter the quality of the product.

A risk assessment should be conducted for each component to evaluate the applicability of the extractable profile data. For components considered to be at high risk to leachables, including those taking up leachables extensively or those stored for longer periods, an assessment of leachable profile studies, including safety concerns, and should be taken into consideration, as necessary.

If applying simulated processing conditions these should accurately reflect the actual processing conditions and be based on a scientific rationale.
Summary & Conclusion

- Quality risk management approach is recommended in regulations
- Quality by design principles are referenced in new guidances
- Global regulatory harmonisation has taken more steps to realisation
- New documentation will be more specific and wider ranging
- Inspection approaches continues to focus on typical issues HOWEVER now includes more citations aimed at drug lifecycle management
- Knowledge and awareness of global trends is critical to achieving and maintaining regulatory and inspectional compliance
Current Key Guidances & Regulations

FDA guidance for industry sterile drug products produced by aseptic processing - current good manufacturing practice

WHO annex 6 good manufacturing practices for sterile pharmaceutical products

EU GMP guide to good manufacturing practice for medicinal products annex 1

PICS Validation of Aseptic Processes

PICS Technical Interpretation to Revised Annex 1 of PICS GMP Guide

ICH Q9 Quality Risk Management

ICH Q10 Pharmaceutical Quality System

NB FDA, EMA / PICS, WHO regulations are supported and supplemented with guidance documents
Thank You for your Attention!

May we be of Further Assistance?

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