BIOTECH

Technical Regulatory Topic

USTR 3875

“EudraLex Annex 1 Manufacture of Sterile Medicinal Products” FAQs and Clarification of Potentially Ambiguous Statements

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1 Introduction

With the official release of "EudraLex Volume 4: EU Guidelines for Good Manufacturing Practice for Medicinal Products for Human and Veterinary Use. Annex 1 Manufacture of Sterile Medicinal Products'" in August 2022, end-users have one year to show compliance with the new requirements outlined in the document. However, even with one of the objectives of the revised Annex 1 document being "to remove ambiguity and inconsistencies", Pall has compiled a list of statements in the newly released Annex 1 document that may warrant further clarification. Pall's interpretation of some of these statements is included here.

2 Annex 1 Section 4

2.1 Section 4.32 – Can Integrity Testing Be Performed on High Efficiency Particle Air Filters?

- "The requalification of cleanrooms and clean air equipment should be carried out periodically following defined procedures. The requalification should include at a minimum the following:
  - Cleanroom classification (total particle concentration)
  - Integrity test of final filters…."

Answer: This may be interpreted to indicate integrity testing of HEPA filters and/or the vent filter in an aseptic process, but most likely applies to HEPA filtration of the classified area or restriction access barrier system (RABS). HEPA filters can be integrity tested and further information can be found at:

https://www.cleanroomtechnology.com/news/article_page/Integrity_testing_of_HEPA_filters_A_practical_approach/150453.

Vent filters can also be integrity tested and should follow the manufacturers standard instructions.

2.2 Section 4.35- If Disinfectants and Detergents are Sterile Filtered, Do I Need to Validate the Process?

- "Disinfectants and detergents used in grade A and grade B areas should be sterile prior to use. …"

Answer: There is no regulatory requirement that a disinfectant that has been sterilized using sterile filtration must have filter validation testing performed. However, if an end-user wishes to have bacterial challenge testing performed as part of their risk assessment, then Pall can perform this testing.

3 Annex 1 Section 5

3.1 Section 5.5 - What Defines Direct and Indirect Product Contact Parts?

- "For aseptic processes, direct and indirect product contact parts should be sterilised. Direct product contact parts are those that the product passes through, such as filling needles or pumps. Indirect product contact parts are equipment parts that do not contact the product, but may come into contact with other sterilised surfaces, the sterility of which is critical to the overall product sterility (e.g. sterilised items such as stopper bowls and guides, and sterilised components)."

Answer: The end-user should evaluate and clarify this with a risk assessment of the process to ensure all relevant contact parts are recognized and sterilized. Pall also recommends that the risk assessment consider the risk of recontamination of already sterilized components.

4 Annex 1 Section 6

4.1 Section 6.7 - What Monitoring and Maintenance of Filters in a Water System is Recommended?

- "… Measures should be taken to minimize the risk of presence of particulates, microbial contamination/proliferation and endotoxin/pyrogen (e.g. sloping of piping to provide complete drainage and the avoidance of dead legs). Where filters are included in the system, special attention should be given to their monitoring and maintenance. … "

Answer: End-users should ensure their water systems are appropriately designed to mitigate the risk of contamination. Implementation of 0.1 µm rated sterilizing grade filters may be appropriate to reduce the potential for contamination by waterborne bacteria, some of which are known to be able to penetrate a 0.2 µm sterilizing grade filter (e.g. *Ralstonia pickettii, Stenotrophomonas maltophilia,* and *Burkholderia cepacia*).

Pall recommends that the differential pressure over the filter is monitored, during use and Steam in Place (SIP) cycles, as well as integrity testing of the filters is performed. In addition, end-users should have a robust preventative maintenance program in place for change out of final filters at the point of use and vent filters on tanks. Additional information may be found in Pall document reference
USTR 3441 "Meeting Regulatory Requirements for Vent Filtration on Water for Injection (WFI) Tanks" (available via the Accelerator℠ Documentation Center) and USTR2330a "Sterile Vent Filtration on Ozonated Water Tanks" (available upon request from your Pall representative).

4.2 Section 6.11 - How Can I Ensure that Pall Hydrophobic Filters are Not a Source of Contamination, and How Do I Perform Integrity Testing Pre- and Post-Use?

- "Where WFI storage tanks are equipped with hydrophobic bacteria retentive vent filters, the filters should not be a source of contamination and the integrity of the filter tested before installation and after use. …"

Answer: Pall recommends that vent filters are sterilized prior to use to mitigate the risk of microbial contamination. Integrity testing can be performed using water intrusion testing on tank vent filters, to assure that these critical filters still have sterilizing capability during long-term operation, or after steam sterilization. Please refer to Pall documents USTR 3441 "Meeting Regulatory Requirements for Vent Filtration on Water For Injection (WFI) Tanks" and USD3033a "Best Practices For Successful Filter Integrity Testing Using The Water Intrusion Test (WIT) Method" available via the Accelerator Documentation Center for further details.

4.3 Section 6.19 - How Should Microbial Monitoring of the Gas be Performed and at What Frequency?

- "Gases used in aseptic processes should be filtered through a sterilising grade filter (with a nominal pore size of a maximum of 0.22 µm) at the point of use."… "When gases are used in the process, microbial monitoring of the gas should be performed periodically at the point of use."

Answer: The requirement for sterile filtration of gases in an aseptic process is not a new requirement, but the requirement for periodic microbial monitoring of the gas is not clear. It could include bioburden monitoring upstream of the sterilizing grade filter and/or bioburden measurements post sterile filtration.

Bioburden monitoring of the gases should follow a set schedule of evaluation, from which alert and action limits can be defined. In addition, the filter supplier can provide data on the removal efficiency of the gas filter and the recommended conditions of use. Little to no bioburden monitoring should be necessary if the gas filter is used according to recommendations. However, if the gas filter is used for extended periods of time, then a risk assessment should be used to evaluate the risk of bioburden. The risk assessment could be supported with baseline bioburden data taken downstream of the gas filter at the end of extended use.

5 Annex 1 Section 8

5.1 Section 8.5 - What Filter Should be Used to Reduce Bioburden Levels and Particles Prior to Filling?

- "Processing of the bulk solution should include a filtration step with a microorganism retaining filter, where possible, to reduce bioburden levels and particles prior to filling into the final product containers....."

Answer: The EU "Guideline on the Sterilisation of the Medicinal Product, Active Substance, Excipient and Primary Container" states "In most situations, a limit of NMT 10 CFU/100 ml (TAMC) would be acceptable for bioburden testing". To achieve this requirement, a bioburden reduction filtration using a 0.45 µm or 0.2 µm rated filter, or a 0.2 µm rated sterilizing grade filter may be used. The decision should be based on a risk assessment. It could also be useful to confirm filter integrity post-use by performing an integrity test. Some agencies or single inspectors may also request a bacterial retention test for validation of that bioburden reduction step.

5.2 Section 8.73 - Does Pall Use Ethylene Oxide for Pre-Sterilized Products?

- [Sterilisation with ethylene oxide] "This method should only be used when no other method is practicable. During process validation, it should be shown that there is no damaging effect on the product..."

Answer: No, Pall does not use ethylene oxide as a mode of sterilization. However, we are aware that some third parties may use this mode of sterilization and incorporate Pall filters in their single-use assemblies, so Pall recommends review of the sterilization mode claimed by the third party.

5.3 Section 8.79 - How Should Compatibility be Assessed During Filter Selection?

- "... The selection of the filter used should ensure that it is compatible with the product and as described in the marketing authorization. ..."

Answer: The filter supplier can assist with filter selection based on expected compatibility of the filter's materials of construction with the process fluid and intended processing conditions. The rationale for filter selection should be documented in a risk assessment. Additional technical information available from Pall (e.g. extractables, particulate data) can also be used in the risk assessment to rationalize the filter selection, including a theoretical compatibility assessment, as required. It is also noted that in some regions (e.g. China), regulatory expectations may include assessment of extractables from packaging materials.

5.4 Section 8.80 - Does this Mean Redundant Filtration is a Regulatory Expectation?

- "... Due to the potential additional risks of a sterile filtration process, as compared with other sterilisation processes, an additional filtration through a sterile sterilising grade filter, as close to the point of fill as possible, should be considered as part of an overall CCS."

Answer: In view of patient safety, the expectation is to have another, or second product sterilizing grade filter (commonly referred as redundant filter) placed close to filling. Redundant filtration acts as a risk-mitigation strategy for critical filtration applications. The redundant product filter is used as a back-up to protect against the possibility of an integrity test failure for the primary product filter. If the primary filter does not meet integrity test specifications, installing a second filter in series will reduce the likelihood that both filters are not integral. In addition, as the second filter in the series is protected by the first filter, the likelihood of masking a defect in the second filter by particles or fouling of the filter during filtration is significantly decreased.

5.5 Section 8.81 - How Can Pall Assist End-Users to Meet this Requirement?

- "The selection of components for the filtration system and their interconnection and arrangement within the filtration system, including pre-filters, should be based on the critical quality attributes of the product, justified and documented."...."Adsorption of product components and extraction/leaching of filter components should be evaluated..."

Answer: As part of the filter selection process, Pall recommends that end-users conduct a risk assessment which should include a prior knowledge assessment (PKA). The PKA can be based on internal studies, supplier information or scientific literature. Product claims specifications (typically documented in validation guides) can be used to demonstrate suitability of the components for the intended application. In addition, Pall recommends that after selection of a filter, the end-user performs adsorption studies to ensure that the product meets the critical quality attributes (in terms of product potency) post-filtration.

5.6 Section 8.82 - Does the Definition of 0.22 µm Filters as Sterilizing Grade Filters Apply also to 0.2 µm or 0.1 µm Rated Filters?

- "The filtration system should be designed to: (…)

  vi Permit in-place integrity testing of the 0.22 µm final sterilising grade filter, preferably as a closed system, both prior to, and following filtration as necessary. ….."

Answer: Yes, 0.2 µm rated sterilizing grade filters are considered equivalent to 0.22 µm rated sterilizing grade filters. The U.S Food and Drug Administration (FDA) Guidance for Industry - Guidance on Sterile Drug Products Produced by Aseptic Processing-Current Good Manufacturing Practice (2004) explains this fact in a footnote: "0.22 µm and 0.2 µm are considered interchangeable nominal pore size ratings". Further, 0.1 µm rated filters can also be considered a sterilizing grade filter and thus equivalent to 0.22 µm filters in terms of performance for sterilization filtration, assuming it was validated as sterilizing grade.

5.7 Section 8.82 - If the Filter is Removed from the Housing for Post-Use Integrity Testing, Is the Test Still Valid?

- "The filtration system should be designed to: (…)

  vi Permit in-place integrity testing of the 0.22 µm final sterilising grade filter, preferably as a closed system, both prior to, and following filtration as necessary. ….."

Answer: In Pall's opinion, post-use integrity testing should be performed with the filter installed in the same housing (for filter cartridges) as a best practice. However, there are situations where the process fluid may be difficult to remove from the filter membrane, and in such cases, use of a lower surface tension reference fluid may be required which may require the filter to be moved off-line. While ideally, post-use integrity testing of a sterilizing grade filter should be conducted in the housing or while the filter is positioned in line, it is also acceptable to have filter integrity confirmed by the filter supplier. If the filter is removed from the housing for the purposes of integrity testing, sealing of the filter cartridge should be confirmed and documented prior to removal.

5.8 Section 8.83 - What Pharmacopeial Requirements does Pall's Filter Validation Testing Program Comply With?

- "Sterile filtration of liquids should be validated in accordance with relevant Pharmacopeia requirements. Validation can be grouped by different strengths or variations of a product but should be done under worst-case conditions. The rationale for grouping should be justified and documented."

Answer: Pall performs filter and single-use technology (SUT) validation testing (in support of core validation and process-specific validation) in accordance with relevant regulatory and industry guidance, including the appropriate pharmacopeial guidance. Pall adheres to the following pharmacopeial guidance as appropriate:

- United States Pharmacopeia (USP) <1229.4> Sterilizing Filtration of Liquids
- USP <87> Biological Reactivity Test, I*n Vitro*
- USP <88> Biological Reactivity Test, I*n Vivo*
- USP <233> Elemental Impurities – Procedures
- USP <665> Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products

- USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems
- USP <1664> Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems
- USP <1665> Characterization of Plastic Components and Systems Used to Manufacture Pharmaceutical Drug Products and Biopharmaceutical Drug Substances and Products
- European Pharmacopoeia (EP) 5.1.2 Biological Indicators of Sterilisation

It should be noted that other guidance may also be followed as applicable (e.g. PDA Technical Report 26 ("Sterilizing Filtration of Liquids"), ISO 13408-2 "Aseptic processing of health care products — Part 2: Sterilizing filtration").

5.9 Section 8.83 - Can Pall Assist with Product Grouping for Process-Specific Filter Validation Testing?

- "Sterile filtration of liquids should be validated in accordance with relevant Pharmacopeia requirements. Validation can be grouped by different strengths or variations of a product but should be done under worst-case conditions. The rationale for grouping should be justified and documented."

Answer: Yes, Pall has extensive experience in rationalizing grouping of multiple products with similar properties. Bracketing of product groups is evaluated on a case-by-case basis but typically products are bracketed according to the product components and relevant upper and lower manufacturing process limits. Contact Pall for further technical rationale and assistance.

5.10 Section 8.85 - If My Sterile Filtration Step is Pressure Controlled, Do I also Need to Monitor Flow Rate?

- "Filtration parameters that should be considered and established during validation should include, but are not limited to:...
  - Maximum operating pressure
  - Flow rate..."

Answer: Regulatory agencies expect filter validation studies to be conducted using the worst-case conditions. "Worst-case" refers to a set of conditions encompassing upper and lower processing limits and circumstances, including those within standard operating procedures, that pose the greatest chance of process or product failure. Pall document reference USTR 3474 "How to Select Worst-Case Parameters for Process-Specific Filter Validation Studies" can be referred to for selection of worst-case parameters for process specific filter validation studies.

Filter validation testing is executed based on the end user's filtration mode. If the sterile filtration is pressure driven, and pressure is being recorded in the batch record, then the critical process parameter is upstream or differential pressure. Hence during validation studies worst case upstream or differential pressure would be simulated. However, during process-specific bacterial challenge testing, both pressure and flow rates are recorded as a requirement to execute the test. Pall is aware that some regulatory agencies have requested end-users to monitor both pressure and flow rate to demonstrate process control.

5.11 Section 8.86 - If My Filtration is Flow Rate Controlled, Does Pressure Differential Still Need to be Monitored?

- "... Results of critical process parameters should be included in the batch record, including but not limited to the minimum time taken to filter a known volume of bulk solution and pressure difference across the filter. ..."

Answer: Pall ensures filter validation testing is executed based on the end user's filtration mode. If the sterile filtration is pump driven, and flow rate is being recorded in the batch record, then the critical process parameter is flow rate. Hence during validation studies, worst case flow rate would be simulated. However, at that worst case flow rate, differential pressure across test filters is also recorded. It is good practice to monitor both differential pressure

and flow rate during sterile filtration during manufacturing to have a controlled filtration step and ensure the filtration is performed within defined parameters.

5.12 Section 8.87 - What is Pall's Position on Performing PUPSIT?

- "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…."

Answer: A post sterilization integrity test provides meaningful data about filter integrity, Pall therefore supports the use of PUPSIT, as described in document reference USTR 3650 "What is the Pall's Position on PUPSIT?" available on the Accelerator Documentation Center. However, it is recognized that there may be cases where PUPSIT may not be possible (e.g. for very low batch volumes or where implementation of PUPSIT could pose an unacceptable risk to the overall process). Therefore, a decision on whether or not to apply PUPSIT should be made on a risk assessment basis. This risk assessment should follow the principles and tools for quality risk management as described in International Council for Harmonisation (ICH) Q9 Quality Risk Management to enable an effective and consistent risk-based decision regarding the quality of the filtered product.

5.13 Section 8.87 - Do End-Users have to Validate the Integrity Test?

- "…The integrity test process should be validated and test results should correlate to the microbial retention capability of the filter established during validation…."

Answer: Filter suppliers have the responsibility to provide a suitable integrity test method that has been validated and that the integrity test values are correlated to bacterial retention (for bioburden reduction or sterilizing grade filters). This information is part of the filter quality dossier, and is shared with end-users in the form of Validation Guides etc. End-users have the responsibility to ensure that integrity testing is performed according to recommended methods using qualified equipment and trained operators.

5.14 Section 8.87 - Can Pall Provide Assistance with Performing Risk Assessments Regarding the Use of PUPSIT?

- "….Points to consider in such a risk assessment should include but are not limited to: …

  iii. In depth process knowledge such as:

  - The specific product type, including particle burden and whether there exists any risk of impact on filter integrity values, such as the potential to alter integrity-testing values and therefore prevent the detection of a non-integral filter during a post-use filter integrity test. …"

Answer: The potential to alter integrity test values and not detect a non-integral filter post-use has been shown to be very low (as demonstrated by the work of the Sterile Filtration Quality Risk Management Biophorum workstream), and unlikely to occur in a full-scale process when the filter would not show excessive fouling. However, Pall can provide recommendations to end-users who may have concerns about this.

5.15 Section 8.87 and 8.88 - If Integrity Testing is Performed on a Filter Off-Line or if the Filter is Removed from the Housing, is the Result Still Valid?

Section 8.87

- "… A sterilising grade filter that is used to sterilise a fluid should be subject to a non-destructive integrity test post-use prior to removal of the filter from its housing…."

and Section 8.88

- "The integrity of critical sterile gas and air vent filters (that are directly linked to the sterility of the product) should be verified by testing after use, with the filter remaining in the filter assembly or housing."

Answer: Ideally, it is best practice to perform the post-use integrity test when the filter is still on-line to minimize further manipulation. It is acknowledged that there are situations when the filter may have to be tested in a different location (e.g. if testing with alcohol as a reference fluid), but Pall recommends keeping the filter in the housing to the extent possible. If the filter has to be removed from the housing and passes integrity testing, the result is valid, and there is no reason to indicate that the filter is not integral. However, removal of the filter from the housing may increase the risk of potential damage to the filter due to excessive manipulation. In addition, sealing of the filter cartridge should be confirmed and documented prior to removal.

5.16 Section 8.94 and 8.95 - What is the Risk of Using a Sterilizing Grade Filter for More Than One Working Day?

Section 8.94

- "Liquid sterilising grade filters should be discarded after the processing of a single batch and the same filter should not be used continuously for more than one working day unless such use has been validated."

and Section 8.95

- "Where campaign manufacture of a product has been appropriately justified in the CCS and validated, the filter user should:

    i. Assess and document the risks associated with the duration of filter use for the sterile filtration process for a given fluid.

    ii. Conduct and document effective validation and qualification studies to demonstrate that the duration of filter use for a given sterile filtration process and for a given fluid does not compromise performance of the final sterilising grade filter or filtrate quality.

    iii. Document the maximum validated duration of use for the filter and implement controls to ensure that filters are not used beyond the validated maximum duration. Records of these controls should be maintained.

    iv. Implement controls to ensure that filters contaminated with fluid or cleaning agent residues, or considered defective in any other way, are removed from use."

Answer: If a sterilizing grade filter has been validated for more than 24 hours and has been shown to be integral via bacterial challenge testing, there is minimal risk of the filter not performing as expected. Addition of the word "continuously" in Section 8.94 might imply that repeat non-continuous use is acceptable but Section 8.95 still indicates that all use must be supported with validation and that the process must be controlled to stay within validated parameters. Ultimately, for a final filter used to sterilize a drug product, the filter/process must be fully validated. In a complex process (such as a continuous process, a 'campaign', or if the filter is reused) the validation is strengthened with a risk assessment which may include performing bacterial challenge testing on used process filters that have been exposed to the full campaign.

5.17 Section 8.129 - What Can Pall Provide to Mitigate the Risk of Potential Failure Modes?

- "… Supplier assessment should include the collation of data in relation to potential failure modes that may lead to a loss of system sterility."

Answer: Pall performs extensive testing as part of product qualification to mitigate the risk of potential failure. Examples include correlation of bacterial retention to integrity testing for sterilizing grade filters, and helium integrity test for single-use systems. This data is used to establish appropriate quality control (QC) release data to mitigate the risks of potential failures.

5.18 Section 8.137 - Does this Mean that the End-User Should Perform Validation Testing to Cover Transportation or Freeze/Thaw?

- "… Attention to the structural integrity of the single use components is necessary where these may be exposed to more extreme conditions (e.g. freezing and thawing processes) either during routine processing or transportation. This should include verification that intrinsic sterile connection devices (both heat sealed and mechanically sealed) remain integral under these conditions."

Answer: Product validation guides provide substantial verification for individual components of a single use system, when used under the validated conditions (e.g. USTR3130b, "Kleenpak® Presto Sterile Connector Validation Guide" gives a detailed description of the tests validating its use). However, it is difficult to completely cover all possible conditions of use on all possible (varied and complex) single-use systems, so it may be necessary to have further validation tests performed, especially for some complex freezing and transporting scenarios. Pall can help with the risk assessment and design of these tests, when needed.

6 Annex 1 Section 10

6.1 Section 10.7 - What Does Pall Recommend to Mitigate the Risks for Short Shelf-Life Products?

- "For some products it may not be possible to obtain a sterility test result prior to release because the shelf life of the product is too short to allow completion of a sterility test. In these cases, the additional considerations of design of the process and additional monitoring and/or alternative test methods required to mitigate the identified risks should be assessed and documented."

Answer: For short shelf-life products, Pall recommends that as early on in clinical development as possible, the end-user performs some preliminary studies to demonstrate that under the intended processing conditions, the filter will perform as expected and fully retain any potential microorganisms. Pall's "Sterility Optimization by Assessment of Risk (SOAR)" program can assist with identifying and quantifying any potential risks. In addition, use of rapid microbiological methods may further mitigate the risk for short shelf-life products.

7 Annex 1 Glossary

7.1 Glossary - Does the Described Testing for Validation (Test Organism and Challenge Level) Apply for Liquid Filters as well as for Gas Filters?

- "Bacterial retention testing – This test is performed to validate that a filter can remove bacteria from a gas or liquid. The test is usually performed using a standard organism, such as *Brevundimonas diminuta* at a minimum concentration of 10^7 Colony Forming Units/cm^2."

Answer: Parenteral Drug Association (PDA) Technical Report 40 Sterilizing Filtration of Gases states "There is no specific standard that defines the retention requirements for a membrane filter used to sterilize gases. There are several approaches to qualifying the retention capability of gas filters, ranging from liquid bacterial retention tests to aerosol challenge tests with bacteria (…). Liquid bacterial challenge testing represents a worst-case condition for sterilizing gas filters because the retention efficiency in liquids is much lower than in gases. Bacterial (spore) aerosol challenges are always less rigorous than a liquid challenge, even though it does represent the way the filter is challenged in a dry gas process."

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