PALL Biotech

White Paper

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A Risk Based Approach to Validation Studies for Sterilizing Filtration and Single-Use Systems

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Contents

1 Introduction

Drug quality cannot be assured only by finished-product testing and process validation is required to establish scientific evidence that a process is capable of delivering an effective and safe drug and does so consistently and reproducibly.

Quality by Design (QbD) was advocated by the FDA as part of the Pharmaceutical Quality for the 21st Century – A Risk Based Approach initiative and it was later addressed in the ICH guidelines [1,2,3,4], the draft Annex 1 of the EU GMP guide [5] and the Chinese Guidelines for the Technology and Application of Sterile Filtration [6] as a standard approach to build quality into pharmaceutical development at the start of the process.

Risk mitigation is central to Quality by Design (QbD) and Quality Risk Management (QRM), and increasingly, ways are sought to build quality into production steps, to reduce risk to the patient. With respect to aseptic processing, this includes a thorough understanding of the design space for sterile filtration and single-use systems.

1.1 A Question Based Review Format

One way of capturing the aspects of science and risk for product quality is to adopt a Question based Review – Quality Overall Summary (QbR-QOS) approach. QbR gives a structure through which the data collected by applying QbD can be presented. So far this has been used for Abbreviated New Drug Applications (ANDAs), but the list of questions could equally be applied to new drug applications (NDAs).

Indeed, the FDA stated in the 2014 document, Chemistry Review of Question-based-Review (QbR) Submissions that although implemented for ANDAs, the QbR format could also be used as a basis for developing a structured QOS for NDAs [7]. The principles of QbR could also usefully be applied in regions not controlled by the FDA.

1.2 The Advantages of a Question Based Review Approach

Robert Iser of the FDA in a presentation “Update on Question-based Review” described QbR as “a step in the right direction” [8] as it encourages clear communication and use of similar language. He goes on to say that the use of common quality standards which are consistent with the QbD paradigm and congruent with risk management approaches, encourages justification for choices made throughout the development and manufacture and increases transparency in the applicant’s thought processes.

Benefits to applicants include:

- Clear communication
- Effective quality assessment
- Common quality standards
  - Standardizes submission expectations
  - Provides clear expectations
  - Provides an opportunity to address critical questions about the product’s design, failure risk, and manufacturing controls from both a performance and patient usability perspective.
  - Reduces questions from the reviewers during the review cycles
  - Use as an internal communication tool

A risk based approach to quality maximizes economy of time, effort and resources and the QbR checklist was developed following these principles. The QbR process can be used as part of the risk assessment approach for sterile filter and single-use system validation.

Using the questions in the QbR checklist to review the validation of a drug process and as a starting point to assess risk, whether for an ANDA or NDA could help manufacturers to maximize the assurance of sterility of their process and meet the expectations of the regulators.

The following notes are grouped around the relevant filter validation questions from the QbR document and are meant to assist with a risk assessment of filter validation.

2 When Should Filter Validation Packages be Prepared?

Typically, the final sterilizing filter and / or single-use system validation packages are submitted when the New Drug Application (NDA) is filed.

For products with known risk factors such as increased risk of bacterial penetration with surfactant solutions, liposomes, lipids or emulsions, a risk assessment at Phase 1 or Phase 2 may be initiated. Filter suppliers can help to evaluate the risk to sterility of any given set of processing conditions before initiating the formal filter validation study. If deemed necessary, studies are performed that can help mitigate potential risks associated with sterile filtration or use of single-use systems until it is possible to perform the final validation study.

Ultimately the decision when to perform validation is the end users' responsibility, however there is growing expectations from regulators to have risk mitigation approaches in place from Phase 1 onwards.

3 Question Based Review Checklist

The FDA has issued various QbR documents [7,9,10] for different product types, the questions below are all related to sterilizing filtration.

3.1 How is the Product Filtered?

Filtration process description, purpose of filtration, number of filters used, the pore size and composition of the filters, the filter manufacturer

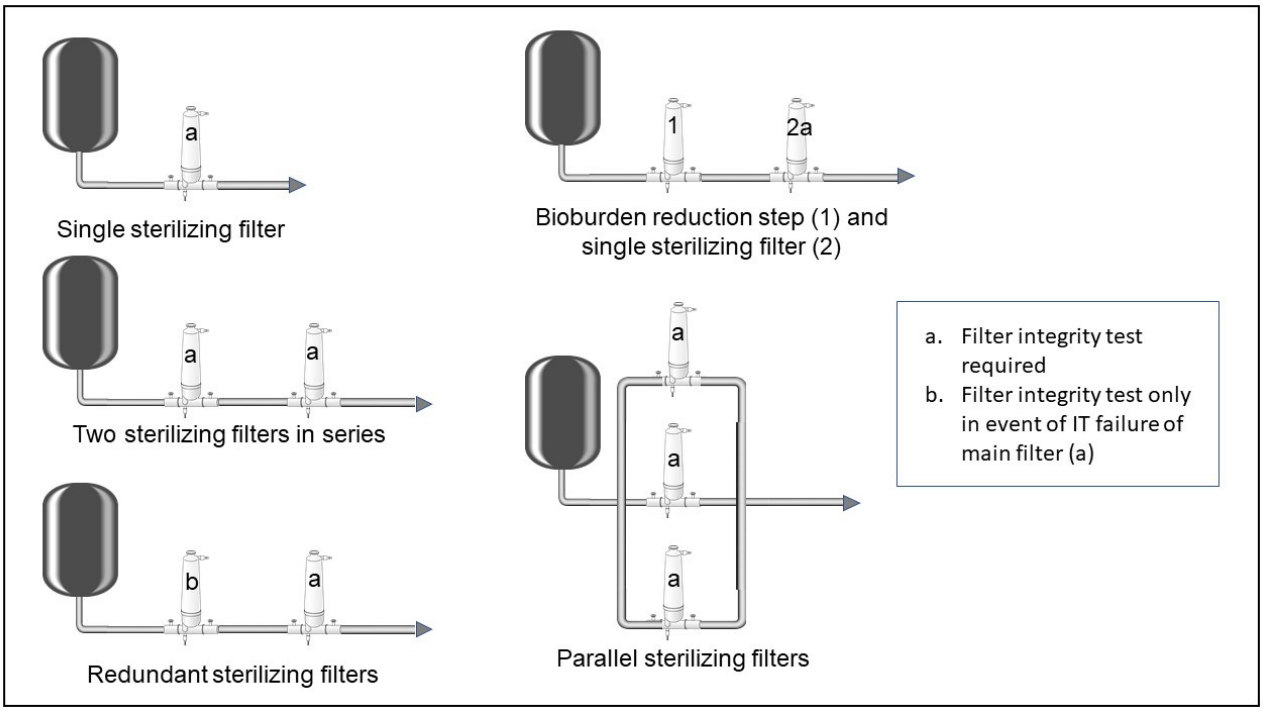
ISO 13408-2 (Aseptic processing of healthcare products - sterilizing filtration) [11] contains an appendix which shows various configurations of sterilizing grade filters which can be used to describe the filtration process, the most common ones are shown in Figure 1.

Sterilizing filter pore sizes are rated as either 0.1 µm or 0.2 µm. While 0.2 µm rated sterilizing-grade filters are most commonly used, 0.1 µm filters may be employed for specific, difficult to filter sterilize fluids (e.g. some liposome formulations), or if the process bioburden may contain mycoplasma or waterborne bacteria which can penetrate 0.2 µm rated sterilizing rated filters.

Information on filter membrane area, pore size and filter composition can be obtained from the filter supplier.

The risk assessment should also include the filter flushing regime, sterilization method as well as operating conditions including system pressures, temperature and filtration time which all contribute to filtration performance as described in PDA Technical Report No. 26 Sterilizing Filtration of Liquids [12].

Figure 1: Common filter configurations



3.2 How is Filter Integrity Examined During Production? And How is the Filter Integrity Measured, Pre-Use and Post-Use?

Industry accepted integrity tests (IT) for sterilizing grade liquid filters are the Forward Flow (or diffusive flow) test and bubble point test. Pall recommends employing the Forward Flow test method for pleated filter devices. For filter devices with a very small filter area and thus very low actual Forward Flow values, Pall recommends the bubble point test method.

The filter device can be wetted with a standard test fluid, such as water, or with the product fluid itself. Product-wetted integrity test parameters can be applied pre-use and post-use, thus minimizing product dilution and flush processes. The principle for determining product wet IT parameters are described in the PDA Technical Report No. 26 Sterilizing Filtration of Liquids [12].

The EU Guide to GMP Annex 1 [5] recommends pre-use, post sterilization integrity testing (PUPSIT) where possible. Implementing integrity testing post sterilization can introduce a risk of breaking the sterile barrier of the process and this needs to be documented as part of the risk assessment. FDA Guidance for Industry [13] only says that pre-use testing can be performed, but does not recommend or mandate it.

If you choose not to perform or the process set-up does not permit a pre-use post sterilization integrity test, an additional risk assessment that adequately justifies the decision should be done.

Whether you are you able to re-process the batch should be considered during both risk assessments. Regulators would likely request supplemental application of reprocessing if this was not anticipated on the original NDA. If reprocessing was incorporated into the NDA detailed procedures and controls beyond those established for routine production is necessary [14]. Is the risk of contaminating the process during the IT test lower than the risk of the filter failing post-use?

3.3 How Do the Filters Used during Filter Validation Compare to the Filters Used during Production?

Bacterial challenge test conditions should simulate the production process, but as they are generally performed in a laboratory, the methodology should be scaled appropriately. 47 mm discs or small filter capsules containing the process filter media are used for bacterial retention and may also be used for adsorption studies.

For bacterial challenge studies, filter media at the low end of the manufacturing specification should be used to meet the regulatory expectations.

For compatibility testing, or generation of product wet integrity test values, the larger filter cartridges or capsules are used.

3.4 What Parameters Were Used during Filter Validation?

Were 'worst case' parameters used in the validation? Typically, filter sterilization conditions, number of sterilization cycles, pressures and flow rates would be considered.

In process-specific filter validation studies, consideration must be given to use worst-case test parameters for the specific application (e.g. maximum filtration time and batch size). There is a useful table in PDA TR 26 [12] which shows process risk assessment factors, but this offers guidance only, and worst-case parameters should be evaluated for each specific application.

The sterilization parameters used in the process (heat sterilization: temperature and duration, gamma irradiation: maximum dose of 50 kGy) should be used for the conditioning of the filter material prior to filter validation testing.

3.5 What Method Was Used to Determine Filter Compatibility during Filter Validation?

In many cases, where validation work for an existing process is being expanded e.g. for an increased batch size or filter size a risk assessment may be adequate based on existing process data and a rationale written to negate the need for further validation testing.

In process-specific compatibility studies, the integrity of a filter device is assessed after exposure to the drug product by a non-destructive integrity test, such as Forward Flow or bubble point test, depending on the filter device employed for the respective study.

The compatibility of the test filter with the process fluid is also addressed in the bacterial challenge study: during this study, the test filter is exposed to the process fluid under the process conditions with respect to exposure time, temperature, flow and pressure and subsequently submitted to bacterial challenge testing, thus confirming that the retention properties of the filter media was not impacted by the exposure to the process fluid.

3.6 What Method Was Used to Determine Filter Extractables during Filter Validation?

Justification for the presence of these extractable materials should be provided.

All product contact components should be assessed for extractables and leachables. A risk assessment decision tree is shown in Figure 2.

A risk assessment might look at where the filter or single-use system is in the process and the further upstream the component, the lower the risk that an impurity will end up in the final product.

USP 665 and BioPhorum Operations Group (BPOG) recommend approaches to model solvents and that suppliers should provide standard data using these solvents which may assist with a risk assessment [15]. A risk assessment may show that standard extractables data provided by suppliers using the BPOG format is sufficient.

If process specific data is required, a model solvent approach may be taken to determine filter extractables. Pall developed a model solvent approach to mimic the drug composition and provide a reasonable worst case for the drug product. It simulates worst-case process conditions, such as exposure time, temperature, sterilization/pretreatment steps, surface area to volume ratio and product extracting properties and is designed to determine the upper-bound level of potential leachables that may migrate from the process equipment into the pharmaceutical formulation or process fluid under standard operating conditions.

Risk assessments should be undertaken as part of the extractables study, including estimating the maximum daily patient exposure of potential leachables and providing independent toxicological assessments of specific impurities.

If warranted by the risk assessment, subsequent leachables studies can be performed with the actual drug product, or closely modeled simulant, to determine the actual levels of previously-identified extractables that migrate into the drug product under actual use. These are typically lower than those determined during worst-case extractables studies.

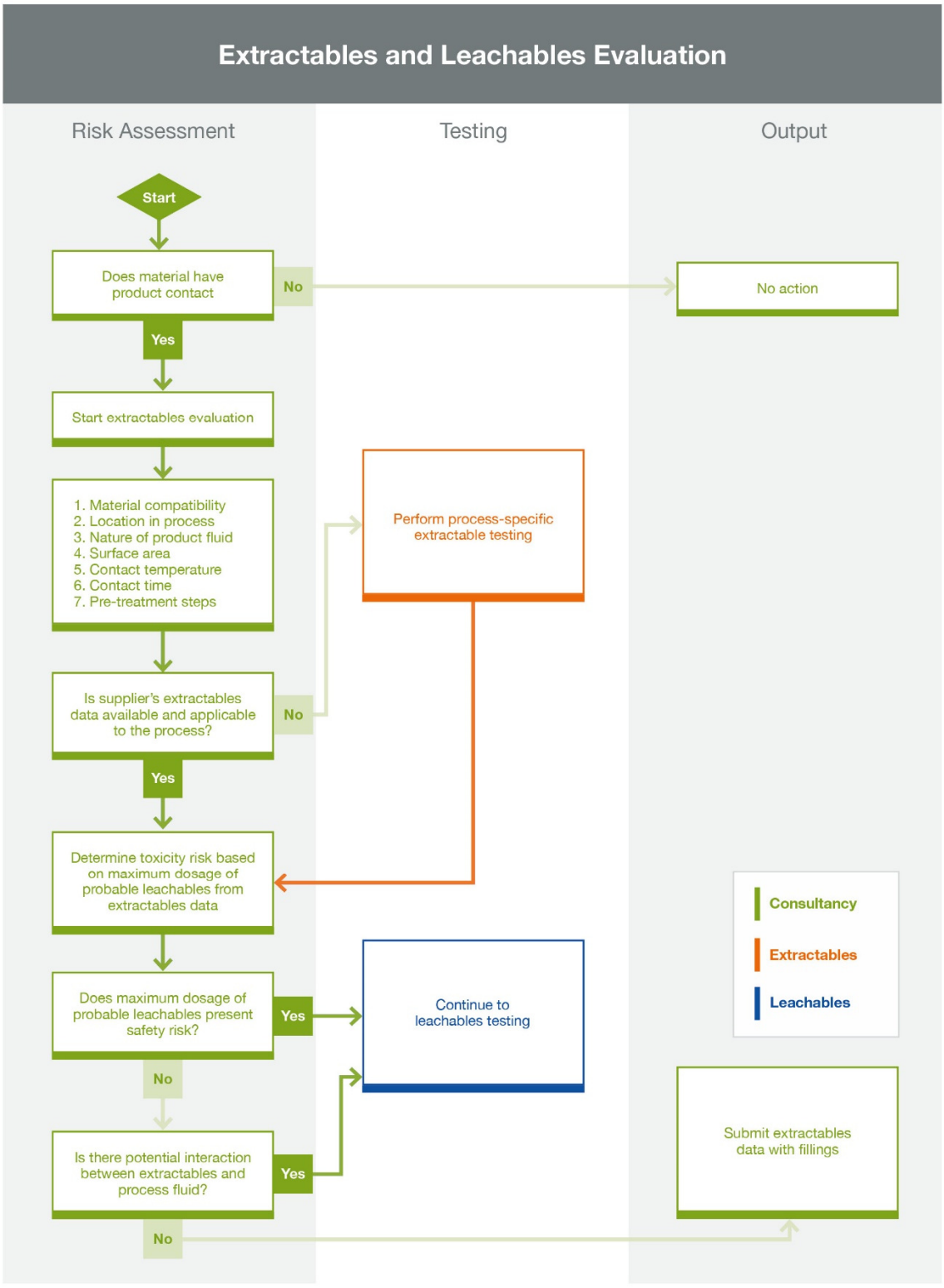
3.7 What Method Was Used to Determine Drug Adsorption to the Filter during Filter Validation?

The majority of adsorption in a filter is due to media membrane which has a much larger surface area than other filter components.

In process-specific validation studies, typically 47 mm discs of the filter media that is used in the production scale filter device are employed. In some cases, small filter devices with that filter media are being employed for these tests. The drug product is filtered and samples taken during the course of filtration.

The samples analysis will typically be carried out by the drug manufacturer as it will be specific to the critical quality attributes of the drug product.

Figure 2: Extractables and leachables evaluation decision tree



3.8 What Method Was Used to Determine Bacterial Retention during Filter Validation?

Which test organism was used? Is the test organism viable in the process fluid? If not, was a simulated product used? If a simulated product was used, provide a description of the simulated product. What was the time the product was recirculated through the filter and the pressure or flow rate used?

In process-specific validation studies, bacterial challenge studies are performed down-scaling from the defined manufacturing process, using a worst-case approach. Typically, *Brevundimonas diminuta* (ATCC 19146) is used as challenge organism; however, bioburden isolates can also be used, if it is expected to be smaller than *Brevundimonas diminuta* (ATCC 19146) when suspended in the drug product. A simulant is used after exposure to the drug product to the filters when the drug product solution negatively impacts the viability of the challenge organism.

For fluids with properties known to foster bacterial penetration through 0.2 µm rated filter media, for example liposome emulsions, a feasibility study may be carried out prior to the process-specific validation study, to evaluate and confirm that the selected filter media candidate is capable of providing a sterile effluent under the process conditions.

3.9 Describe the Method Used to Determine Filter Integrity during Filter Validation

In process-specific bacterial challenge studies, a non-destructive integrity test, such as Forward Flow or bubble point test, depending on the filter device, is used to assess filter integrity prior to and after challenge. For the typically used 47 mm discs, bubble point testing is employed.

4 Conclusion

Using the questions in the QbR checklist to review the validation of a drug process and as a starting point to assess risk, whether for an ANDA or NDA could help manufacturers to maximize the assurance of sterility of their process and meet the expectations of the regulators.

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