



Sterile Filter Validation

When Should Filter Validation Be Performed?

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Although it is widely recognized that product and process related filter validation studies must be performed for aseptic processing, there is no specific guidance that categorically states when such filter validation studies should be performed. Consequently, the decision when to perform filter validation is determined largely by the end-user. 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.

FDA Guidance for Phase 1 Investigational Drugs [1] states that 21CFR GMP "requires drugs, which include Investigational New Drug (IND) products, to comply with current good manufacturing practice". This means that the clinical batch is produced using a sterilizing grade filter which has an integrity test that is correlated to microbial retention (demonstrated by retention of *Brevundimonas diminuta* at a concentration $\geq 1.0 \times 10^7$ colony forming units per cm^2 of effective filtration area ($\geq 1.0 \times 10^7$ CFU/ cm^2)).

Annex 13 of the EU Guidelines to Good Manufacturing Practice [2] states "Production processes for investigational medicinal products are not expected to be validated to the extent necessary for routine production but premises and equipment are expected to be qualified." As with the FDA Guidance for Phase 1 Investigational Drugs, this implies only that use of a qualified (by the filter manufacturer) sterilizing grade filter is required.

Annex 13 further states "For sterile products, the validation of sterilizing processes should be of the same standard as for products authorized for marketing." It is Pall's opinion that this does not mean that filter validation studies are warranted at this early stage of drug development. Further, FDA Guidance for Industry, INDs for Phase 2 and Phase 3 Studies [3] clearly states that for Phase 2 and 3 Studies, "Information related to the validation of the sterilization process need not be submitted at this time". Typically, the final filter validation package is not submitted until the New Drug Application (NDA) is filed [4].

Although end-users are encouraged to apply QbD into new sterile processes as early as possible, there may simply be too many unknown factors related to the final aseptic manufacturing plans. For example, at Phase 2, it is highly unlikely that the production design space will be sufficiently elucidated to select worst-case parameters for filter validation testing.

Therefore, Pall recommends that a risk assessment is performed during Phase 2 clinical trials to review any potential risks for sterility assurance. If the risk is deemed sufficiently low, then the end-users may choose to perform filter validation studies in Phase 3 or when ready to submit their NDA. For end-users who proactively want to apply QbD into sterile filtration at Phase 2, perhaps because the intended process has a higher risk, then they could opt to do screening studies to evaluate any potential risk to the patient in terms of sterility.

Ultimately, timing for performing filter validation studies is the decision of the end user. There may be some exceptions to the information provided here, especially if the process or fluid has an increased amount of risk associated with it. Under such circumstances, Pall encourages the end user to start discussions with the filter manufacturer and regulatory authorities during Phase 2 production.

References:

1. Guidance for Industry CGMP for Phase 1 Investigational Drugs, U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER) Center for Biologics Evaluation and Research (CBER) Office of Regulatory Affairs (ORA), July 2008.
2. EU Guidelines to Good Manufacturing Practice. Medicinal Products for Human and Veterinary Use, Annex 13. Investigational Medicinal Products, February 2010.
3. Guidance for Industry INDs for Phase 2 and Phase 3 Studies. Chemistry, Manufacturing and Controls Information. U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (CDER), May 2003.
4. Guidance for Industry Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products. Center for Drug Evaluation and Research (CDER) Center for Veterinary Medicine (CVM), May 2003.



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