

Simplifying the Validation Process For Sterilising, Microbial and Particulate Grade Filter Products

The validation of a new filtration process or the modification of a filter type used in an existing process can appear a daunting prospect. However, with a structured approach validation costs and time-scales can be managed and minimised.

What do the regulators require?

The FDA in the USA, EMEA in Europe and the MHLF in Japan issue references mainly associated with filter sterilisation of drug products, examples being the FDA's Guideline on Sterile Drug Products Produced by Aseptic Processing 1987 (Reprinted 1991), and sections of the EMEA's Vol. 4. GMP: Medicinal Products for Human and Veterinary Use. Guidance regarding the validation of prefiltration products however is not so readily documented.

Further useful guidance, particularly for FDA approved manufacturers, is found in Scale-Up Post-Approval Changes (SUPAC), Bulk Actives Post-Approval Changes (BACPAC) and Post Approval Changes Sterile Aqueous Solutions (PACSAS) documents. The aim of these documents is to define FDA-recommended testing and filing actions to be taken by a pharmaceutical firm when it changes the manufacturing processes of a drug product that has been approved via a New Drug Application (NDA), an Abbreviated New Drug Application (ANDA), or an Abbreviated Antibiotic Drug Application (AADA). 21CFR314.70 already provides instructions for how changes to approved manufacturing process should be reported to the Agency and the main purpose of the Guidance is to provide industry with clear, streamlined ways to test and report those manufacturing changes, which include changes to filtration processes.

Validation Guidance References:

The core guideline document referenced for validation of sterile filtration processes is the Parenteral Drug Association's (PDA) Technical Document No. 26, Sterilising Filtration of Liquids, issued in 1988. This document is perhaps the most often referenced in discussions on Filter System Validation.

Sterilising Grade Filters are still defined by the pharmaceutical industry as 0.22µm (or smaller) rated membrane filters with an ability to sterilize a fluid containing 10⁷ Brevundimonas diminuta organisms per cm² of effective filtration area.

No such definitions exist for other ratings of filter, although filter manufacturers will define their own testing standards and performance parameters.

The impact of the use of filtration in a process must be assessed against a number of parameters. As part of the development process for a particular filter type, base parameters are tested and verified for the product by the manufacturer.

The results of this testing program serve to provide base data to a filter user and are normally supplied in a base validation support document.

However this testing cannot possibly simulate all conditions to which a filter may be exposed during an actual process.

Process / Product Specific Filter Validation is increasingly expected of filter users by the regulation authorities for most, if not all, filter applications. This has had an impact on some older manufacturing processes, where perhaps the validation process was less stringent at the time of process development, and hard data is unavailable.

Processes are also now being re-validated as new technology is being introduced by filtration suppliers, for example with the introduction of newer membrane materials such as Polyethersulphone (PES).

Areas to be reviewed during the assessment of a sterile filtration process are as follows:

A structured approach can be used to design the Validation process resulting in a validation plan that can be applied to the process.

The flow-chart below is an example of a simple guide to the steps in a validation process:

As an example of a specific structured protocol, consider the sterile filtration of antifoam used in a microbial fermentation facility producing bulk insulin.

Antifoam is a high viscosity solution that is injected into a fermentation process, typically in a number of pulses throughout a batch operation, to minimise formation of foam.

Whilst not a classical SVP sterile filtration, pulsed flow with a high viscosity solution may be considered a worst-case application for a sterilizing grade filter and when combined with extended exposure of the filter to the process for 12-weeks, this is a sterile filtration process with significant operational issues requiring validation.

Following the flowchart, the Validation Plan is shown in the schematic below:

This Validation Plan was adopted following close consultation between domnick hunter's Validation Engineers and the validation department of the Insulin manufacturer. It was this close consultaton which identified early in the process that viability and colony morphology of B. dim in the antifoam was a significant issue in the design of the validation, this needed to be fully understood and characterised using support data. A strategy involving filter conditioning followed by a standard bacterial challenge was justified with this data, simplifying the process. In this case the full-scale process was simulated in domnick hunter's Laboratories using smaller scale filter products than were used in process. The validation was performed initially over a 4-week period to allow the manufacturing facility to begin full-scale operation, with subsequent validation after the full 12-week exposure.