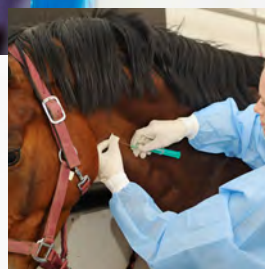


VAN BORSELEN FILTERS



Validation Services

for the Pharmaceutical Industry



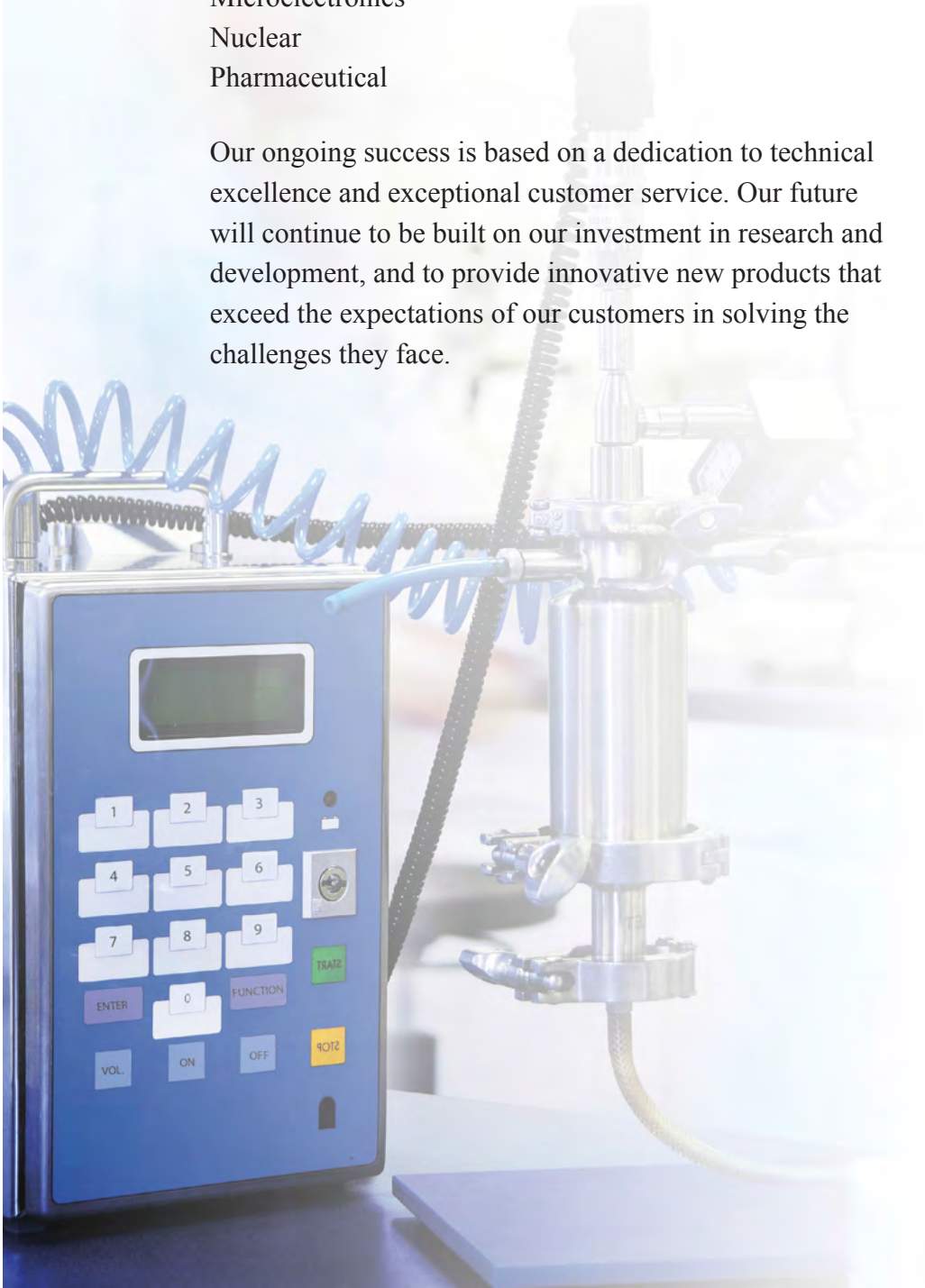
Van Borselen Filters

Van Borselen Filters is an international leader in the development and supply of filtration and separation products.

Van Borselen has an extensive network of manufactureres and partners throughout the world. Our expertise is wide and varied, with products used in markets such as:

Water
Aerospace and Defence
Food and Beverage
Gasification
Microelectronics
Nuclear
Pharmaceutical

Our ongoing success is based on a dedication to technical excellence and exceptional customer service. Our future will continue to be built on our investment in research and development, and to provide innovative new products that exceed the expectations of our customers in solving the challenges they face.



Validation Services

Van Borselen Filters' polymeric and disposable cartridge filters meet international standards for safe application into pharmaceutical processes.

In addition, many pharmaceutical processes also require specific validation in order to guarantee the sterile filtration of a final product.

Van Borselen ensures that all validation studies are performed taking into account the critical parameters and worst-case conditions of these processes.

Our studies adhere to the standards and guidelines established by regulatory authorities (Food and Drug Administration (FDA) and EU) and the recommendations of the Parenteral Drug Association's Technical Report No 26 'Sterilizing Filtration of Liquids'.

Our validation experience encompasses a broad range of injectable products and their manufacturing processes, these include:

- antibiotics
- vitamins
- aggressive-solvent and oil-based formulations
- high viscosities and pressure differentials
- exposure time of up to 80 hours.



Validation requirements

Depending on the process requirements the following validation options are available:

- filter compatibility assessment
- bacterial challenge testing
- extractables analysis
- adsorption studies
- product wetted integrity test studies.

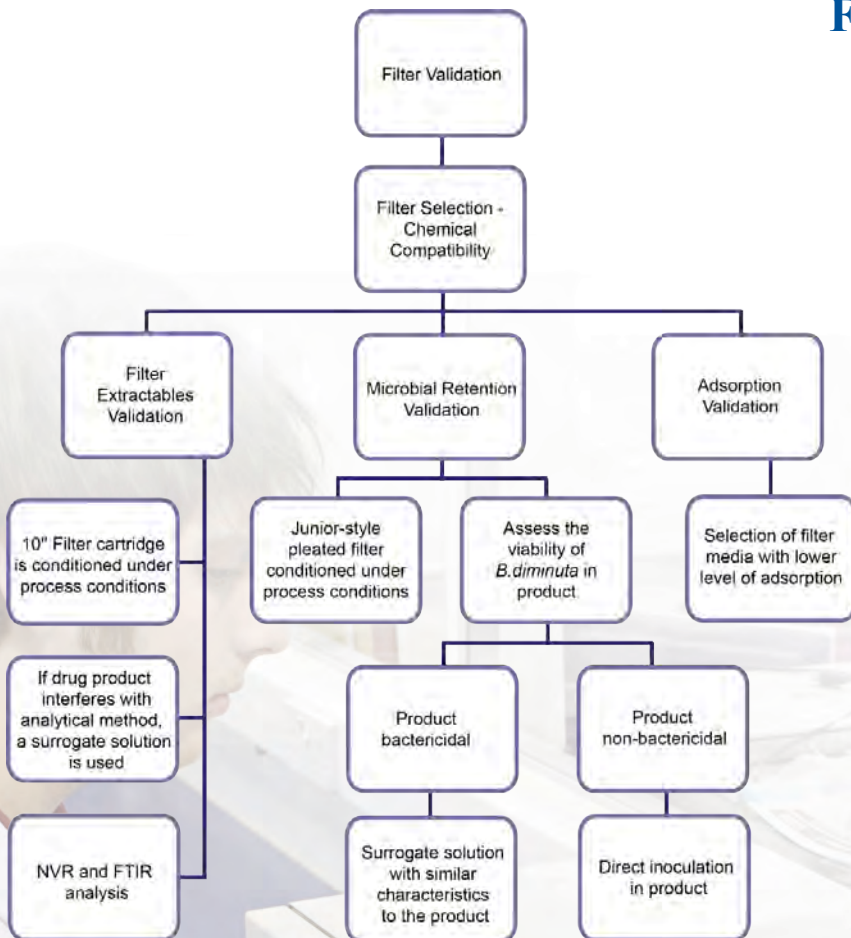
During validation, our philosophy is to mimic the process as closely as feasible:

- We employ pleated filters, recognising that flat membrane-based testing will not replicate the pleated product under flow conditions (e.g. pleat movement and degradation at peaks and troughs).
- Exposure to the product with the maximum contact time and temperature of the process to ensure the integrity of the membrane is not compromised.
- Chemical compatibility of O-rings.
- Analysis of extractables in worst-case process conditions (maximum circulation time, temperature, pH) at an independent laboratory.
- Conditioning of filters under worst-case process conditions before bacterial challenge testing.



Validation Processes

Filter compatibility assessment



Filter compatibility assessment is the first phase of a validation study. This test evaluates the integrity of the filter media and seals after exposure to the product under the worst-case process conditions.

The membrane filters are tested for bubble point, tensile strength and porometry before and after exposure to the product.

The bubble point is correlated to the integrity of membrane since it can detect any large pores caused by the degradation of the membrane, following contact with the product.

Tensile strength can be indicative of whether the product adversely affects the physical properties of the membrane, by a significant decrease in strength or ductility. The O-ring's incompatibility is indicated by a change in its colour, deformation and weight. Porometry measures the pore size distribution and can give an indication of any potential compatibility issues.

Bacterial challenge testing

Bacterial challenge testing is performed at an independent, FDA approved laboratory. The objective of bacterial retention is to demonstrate the ability of a filter to produce sterile product in a specific pharmaceutical process.

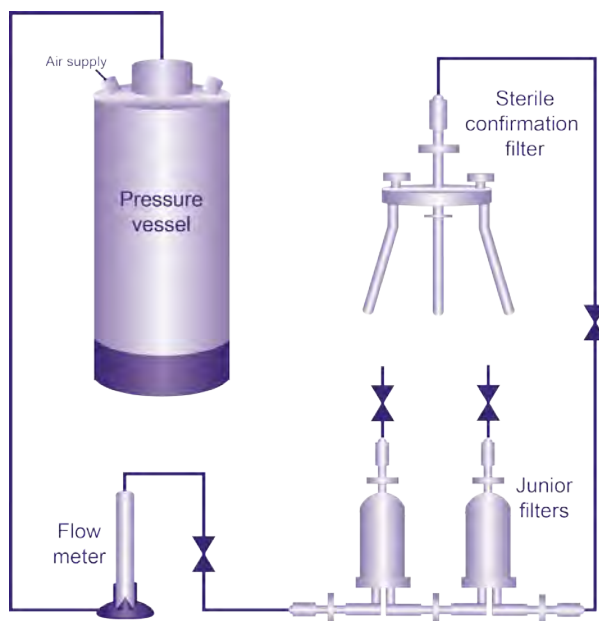
At least three filters cartridges, from different batches, are required to be preconditioned with the product under actual processing conditions including: flow rate, pressure, temperature and time.

One of these filters has an integrity test result close to the specification of a filter as a worst case scenario. The challenge organism *Brevundimonas diminuta*, is grown in accordance with the ASTM standard F838, in order to reach a small size and produce mono dispersed cells. A positive control filter cartridge, with a 0.45µm pore rating, is run in parallel with the test filters in order to ensure the organism's viability and size, and that there is no aggregation of cells.

The bactericidal properties of the product need to be assessed; the viability is verified by direct inoculation into the product and should mimic the actual process time and temperature.

Where the product is found to be toxic to the challenge bacteria, a non-bactericidal surrogate is selected. The test is performed with a concentration $> 1 \times 10^7$ colony forming units (CFU)/cm² of filter area, with an acceptance criterion of zero colonies in the filtrate.

Set-up for bacterial challenge testing



Extractables analysis

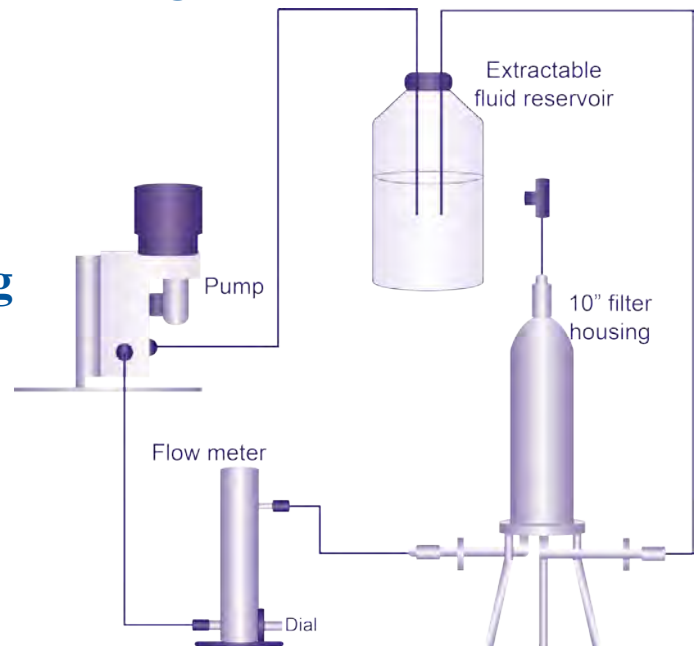
Extractables are physical or chemical compounds that can be released by the filter and seals within a specific system, under extreme conditions (e.g. aggressive solvents, temperature, long filtration runs).

Typically, the extractable study cannot be performed in the actual product since it would interfere with the analytical method. Therefore a surrogate (model solvent) with similar fluid properties should be used.

The extraction study is designed to replicate a worst-case scenario of the actual process conditions, with respect to key factors such as temperature, time and pH.

The non-volatile residue (NVR) analysis is performed in accordance with USP <661> in order to quantify the amount of extractables released by the filter system. If there are sufficient extractables, following NVR analysis, these are analysed by FTIR spectroscopy.

Set-up for bacterial challenge testing



Validation Processes

Adsorption studies

The level of adsorption by the filter should be minimised to ensure that after filtration, the product contains all of the ingredients within specification.

Filter media can bind preservatives used within the manufacture of solutions for ophthalmic applications (e.g. benzalkonium chloride), and this can lead to an unpredictable shelf-life.

The surface characteristics of the membrane and the process conditions (flow rate, contact time and batch size) have a significant impact on preservative binding.

Van Borselen and its partners have developed an in-house capability, to test the level of adsorption of these preservatives with different filter membranes (under the specific process conditions).

The test results ensure the selection of the correct filter media to guarantee the lowest level of binding, for a specific product, in order to enable an adequate shelf-life and minimise product loss.

Product-wetted integrity testing studies

Integrity testing of sterilizing grade filters pre- and post-use is essential to guarantee the sterility of a product. In some cases, it is more convenient to use the product instead of the reference liquid (usually water or IPA water) as a wetting fluid for integrity testing.

The product-wetted integrity studies are performed by comparing the integrity test results using the product as the wetting agent and the reference wetting fluid on the same filters.

The product-wetted parameters can be determined as: minimum bubble point, test pressure and maximum allowable diffusive flow. The study is performed using at least three filter samples from different batch numbers. The integrity test parameters are influenced by the surface tension and temperature of the product.

Please note: The protocol and test methodology need to be discussed and approved with the test laboratory. A final validation document is provided to the customer, incorporating both Van Borselen's findings and the independent test laboratory's reports.

Cleanroom location



Quality

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Additional Information

Range

Van Borselen Filters Supplies a full range of filtration products: e.g.:
Filtercartridges (Meltblown/ Membranes/ Activated Carbon)
Filter housings, Filterbags, Lenticular Module Filters, Self Cleaning
Filters, Filter Sheets, Sieving Machines, Porous Sintered Metal,
Oil skimmers, Strainers and many more..

Material Conformity and Validation

The bio-safety of all materials used in the manufacture of all our Borso-range filter cartridges is assured by FDA approval to Title 21CFR.177. and EC 10/2011

Quality control

Our factories are all located in Western Europe and are accredited to ISO 9001-2008.

All our filters are fully traceable and manufactured under clean room conditions.

Engineering capacities

One of our strengths is developing filter vessels for critical applications in the chemical industry.

We have a wide experience in supplying filter vessels, like Duplex (UNS S31803), Super-Duplex (UNS S32750/60), Titanium, RvS316L, CS (optionally with a coating or lining).

Our filter vessels comply with the necessary design codes (ASME VIII, EN13445, U-stamp and PD5500) and comply to ATEX and PED 97/23/EC standards. Both liquids and gasses PED classes I, II, III, IV, all modules



APPROVED



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