Minimising risk through validated filter performance

Cartridge filtration is widely used to provide microbial stability of wine during the filling operation. Often referred to as 'sterile' filtration, how do you know that the filter is doing its job? Methods such as bubble-point and pressure hold integrity tests can give an indication that the filtration membrane is intact. However, any test is meaningless unless it can be correlated to the filter's ability to remove spoilage organisms.

This article explains the process by which filter manufacturers should validate their products to ensure that they are fit for purpose and thereby provides some guidance regarding your choice of membrane filter for your process. It unashamedly explains the theory behind integrity testing and 'sterile' filtration to emphasise the importance of ensuring that your chosen filters and adopted test method provide meaningful results that assure the performance of your filter, the quality of your product and protects your brand reputation.

Figure 1 – 'Sterilising' grade membrane filters are available in various formats to suit the application. Cartridge filters such as those shown are most commonly used.
Courtesy: Parker Bioscience Filtration Division

What is a filter integrity test?

An integrity test is any method that can be used to non-destructively test a filter's ability to fulfil the function that it was designed for. At point of use, integrity testing is usually only applicable to microporous membrane filters that are used to remove microorganisms from the process stream. Therefore, the integrity test is only meaningful if, during validation of the filter, the test method applied has been correlated to its ability to remove those organisms.

What is 'sterile' filtration?

Personally, I'm not a fan of the term sterilisation being applied to wine or other beverages. By definition, sterilisation is the removal or killing of all living organisms. The majority of beverages only require removal of spoilage (eg wine, beer) or pathogenic (eg bottled water, dairy) organisms.

The adopted global standard for defining sterile filtration of a liquid is the Parenteral Drug Association's Technical Report No. 26 2008 "Sterilizing Filtration of Liquids". This describes a method to carry out a destructive bacterial challenge test that defines a 0.2 micron sterilizing grade filter as one that is capable of removing 10 million live cells of the bacterium *Brevundimonas diminuta* per square centimetre of filter area. Applied primarily to pharmaceutical processing, if used to filter wine, this grade of filter would irreversibly alter the wine's desirable characteristics. So, in the case of wine and other beverages, the term microbial stabilisation would better suit the removal of all spoilage and pathogenic organisms. However, 'sterile' filtration has been widely adopted in vinification and brewing, so I've given up arguing – just note the inverted commas when I use the term!

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The PDA test procedure cited above can be adapted to test the ability of other grades of membrane filter to remove alternative organisms. For example, *Serratia marcescens* is widely used to define a 0.45 micron pharmaceutical membrane, but this is not representative of microorganisms which are going to lead to problems in winemaking. Instead, a better approach to developing a filter to protect your wine is to validate it using typical spoilage organisms recognised in the industry such as *Brettanomyces, Lactobacillus* and *Acetobacter* species.

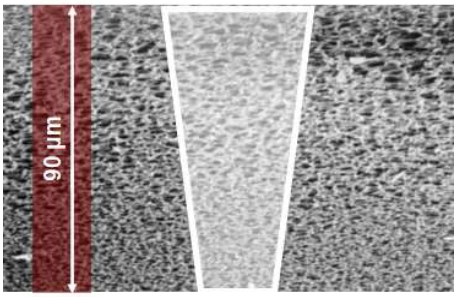

Figure 2 – Cross section through a polyethersulphone microporous membrane. In this case the membrane is asymmetrical with pore size decreasing through its depth. This helps extend service life of the filter.

Design-stage filter validation

Due to the large numbers involved, the retention of microorganisms is normally expressed as a log reduction value (LRV), which is calculated as:
LRV = $\log_{10}$ (No. of cells in / No. of cells out).

For example, if ten million live cells hit the filter and one cell was able to penetrate, the LRV would be 7, equivalent to 99.99999% removal.

The bacterial challenge test involves inoculating a nutrient broth with the test organism and nurturing it until levels are sufficient to challenge each square centimetre of membrane area with a minimum of ten million live cells. The challenge suspension may be adjusted to stress the organisms, for example by the additional of alcohol to reduce their size. The number of organisms that pass through the filter are counted and an LRV is calculated. In order to be classed as 'sterilising' against the test organism, the filter should exhibit full retention. The testing can be carried out on the microporous membrane as produced but should also be repeated on the final constructed cartridge filter to ensure that the membrane can withstand the manufacturing process.

Organism	LRV when challenged with a minimum of 10^7 cfu per cm^2		
	0.45	0.65	1.2
Saccharomyces cerevisiae	FR	FR	FR
Brettanomyces bruxellensis	FR	FR	FR
Lactobacillus brevis	FR	FR	2.0
Acetobacter oeni	FR	FR	7.6
Pseudomonas aeruginosa	9.1	8.9	4.8
Serratia marcescens	FR	FR	2.4

*FR - Fully retentive during challenge

Figure 3 – Extract from a filter datasheet showing the retention of various grades of membrane to wine spoilage organisms. *Pseudomonas aeruginosa*, the smallest pathogenic organism listed in drinking water standards and *Serratia marcescens*, historically used in the pharmaceutical industry, are included for cross reference.
Courtesy: Parker Bioscience Filtration Division

Once the manufacturer has developed the right grade of membrane for the application and has confirmed that it can be constructed into cartridge form, various other tests need to be undertaken to ensure that the cartridge filter meets its performance specifications in other aspects. These should include:

- Extractables tests according to United States and European requirements for food contact.
- Determination of the maximum allowable differential pressure at various temperatures.
- Checking the compatibility of the filter with typical cleaning chemicals that it may contact during use.
- Carrying out steam-in-place or autoclave tests as a means of sterilising the filter before use.

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Continuous validation

All of the tests mentioned so far are destructive so once carried out, the filter is rendered unusable. Ongoing destructive testing should still be carried out against a qualified sample plan, but more regular testing using a non-destructive method will increase confidence that the manufacturing process is under control and, applied at point of use, will assure the efficacy of the filter before use. There are two forms of testing that are widely recognised for membrane filters.

1. Bubble-point test

This test is a good method for small format filters, such as discs, that contain a few square centimetres of membrane area. It is widely used during manufacture of the microporous membrane to check consistency across the length and width of the membrane sheets. It relies on the porous structure of the membrane acting like millions of capillaries that will naturally hold a film of water within the membrane depth. In order to displace the water, air or nitrogen pressure can be applied until the pressure overcomes the interactive forces between the water and the pore walls of the membrane at which point mass flow of gas occurs through the pores. This is termed the bubble-point pressure and can be used to define the pore size of the membrane.

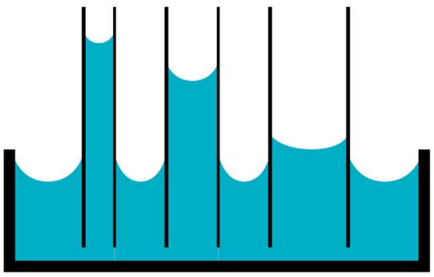

Figure 4 – Capillary action. The interactive forces between the liquid and the walls of a capillary increase in strength as tube diameter decreases. This phenomenon is the basis for integrity testing microporous membrane filters.
Courtesy: Parker Bioscience Filtration Division

The gas will displace the water from the largest pores first, so with some modification, the test can be used to determine the pore size distribution of the membrane.

2. Diffusional flow test

In this case, gas pressure is applied to the wet membrane, but not enough to achieve bubble-point. At low pressure, negligible diffusional flow occurs so the test pressure used is typically around 70–80% of the minimum specified bubble-point of the membrane. At this pressure, the gas dissolves in the water at the high pressure interface and diffuses through to the low pressure side of the membrane from where it escapes. By correlating diffusional flow to the ability of a membrane to remove spoilage organisms, the manufacturer can specify a maximum allowable diffusional flow for each of their filter types.

The various stages of gas flow are shown by the curve in Figure 5 where the wetted porous structure of the membrane is represented by capillary tubes. In this case, the gas flow increases linearly up to around 1.5 bar, at which point the flow begins to increase more rapidly. This represents the transition zone where the largest pores reach bubble-point and mass flow of gas begins.

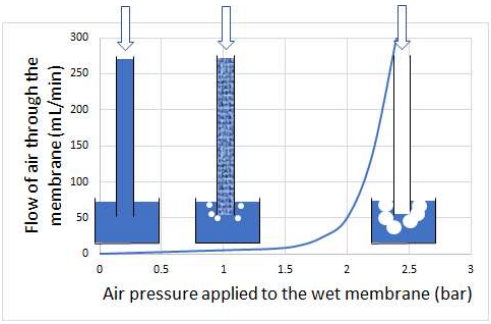

Figure 5 – The relationship between gas flow through a wet membrane, represented by capillary tubes.
Left: At low pressure, diffusional flow is negligible.
Middle: Diffusional flow tests are usually carried out at 70-80% of bubble-point pressure.
Right: Beyond the transition zone (in this case 1.5 – 2.0 bar) water is displaced and mass flow of gas occurs.

In a large format filter, such as a pleated cartridge filter, it is very difficult to determine the difference between high levels of diffusional flow and the transition to bubble-

point, which renders the bubble-point test very inaccurate for cartridge filters.

Practical aspects

The normal format for point of use filters during wine packaging is one or more cartridge filters in a stainless steel housing. The high area of membrane in these systems, as previously stated, complicates the application of the bubble-point test method.

Very sensitive flow transducers, which can be expensive and temperamental, are required to measure diffusional flow directly. It is easier to measure the gas pressure on the inlet side of the filter. If this is isolated, the diffusional flow of gas through the membrane causes the pressure to fall, termed pressure decay. The allowable pressure decay can be calculated from the manufacturer's specified maximum diffusional flow rate using a simple equation that accounts for the upstream volume of the filter housing. An accurate pressure decay value can be determined using specialised electronic equipment, or a rough and ready simple pressure hold test can be carried out using a pressure gauge.

Figure 6 – Integrity test instruments can measure pressure decay with millibar sensitivity and convert to diffusional flow. They are available with different degrees of functionality with some that can carry out a fully automated integrity test
Courtesy: Parker Bioscience Filtration Division

Summary

The key points when choosing cartridge filters for your process are:

- Can the manufacturer demonstrate a rugged and ongoing validation program for the filters?
- Can the manufacturer provide a statement and evidence to confirm that the filter conforms to European food contact requirements for alcoholic beverages?
- Is the recommended integrity test method diffusional flow rather than bubble-point?
- Where designed to remove spoilage microorganisms, has the filter been validated using industry-relevant organisms.

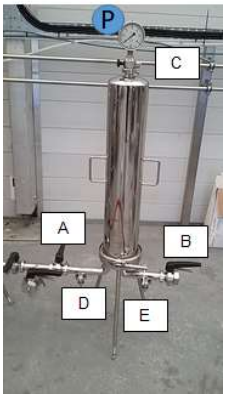

Figure 6 – Example set-up for a simple pressure hold test or a pressure decay test.
P = pressure gauge or integrity test instrument.
A = process inlet valve.
B = process outlet valve.
C = gas inlet valve.
D = inlet drain valve.
E = outlet drain valve.

About the author

Peter Riddell has been involved in filtration and process engineering for over 35 years. Most of that time was spent at domnick hunter Process Filtration (now Parker Bioengineering and Filtration). Initially responsible for developing products for applications across all industries, he was tasked with introducing a range of filters specifically for food and beverage applications which he then went on to support technically and commercially around the world. In 2015, he left Parker to form Integrated Processing Technologies Limited. IPTL operates in the UK F&B industry as a specialist technical support and distribution partner for Parker as well as partnering with a number of other world class manufacturers of filtration, tank cleaning and complementary process components.

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