GE Healthcare

NFF Integrity Testing

28-9137-76 AA

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Introduction

Microporous filter products are used by a number of industries to achieve required levels of purity in both gases and liquids. The verification of filter performance has been identified as an important process monitor in several industries, especially in those applications where product sterilisation or microbial bioburden reduction is required. This has led to the development of a number of integrity test procedures, based around industry preference such as in the beverage sector or regulatory definition as in the pharmaceutical industry.

Integrity testing offers non-destructive methods for proving the capability of a filter product to meet its stated performance when it is installed in an application. This gives confidence to filter users that both before and after filtration processes the installed filter will achieve the required performance. In particular, integrity tests enable users to verify that no filter damage has occurred during storage, installation into the filter housing or following procedures such as chemical cleaning or in-situ steam sterilisation prior to use or during the subsequent manufacturing process.

GE Healthcare - Setting the standard

GE Heathcare bring extensive experience through our scientists, engineers and sales representatives to the process of offering specific filtration systems to meet the needs of your production process. Support services are available covering a wide range of activities including scale up advice from laboratory through pilot scale to production systems, validation support, design and manufacturing of custom housings and filtration products and on-site technical support.

Committed to quality

Quality is of paramount importance to GE Heathcare. As such GE Heathcare has been certified to ISO 9001 since 1987, providing a quality management system that covers the entire organisation from R&D, production, warehousing, materials management and customer support. In addition, our manufacturing facilities operate to the principles of cGMP.

This commitment is underlined by our registration to ISO 14001 during 2001 and our move to ISO9001:2000.

Validation and product certification

To certify that GE Heathcare products meet the required regulatory and quality standards of the industries we supply, all filters are supplied with a certificate of conformance. These certificates are linked to validation guides for both pre-filter and sterilising grade membrane filter cartridges that define methodologies and data appropriate to each filter type. This information typically includes:

- technical specifications
- biological safety testing including Current USP<88> Class VI - 121 °C Plastics
- extractable testing including 21 CFR 211.72 and 210.3(b), (6) for fibre releasing filters
- effluent quality including TOC, bacterial endotoxins, water conductivity and particle release
- chemical compatibility information
- thermal stability
- correlation of a non destructive integrity test to a defined bacterial challenge

Where appropriate these data are included in the GE Healthcare Drug Master File – DMF 7564 at the U.S. Food and Drug Administration (FDA).

Validation support services

GE Heathcare has extensive laboratory facilities and trained personnel capable of providing a range of validation support services to support manufacturers meet their requirements for process validation relating to the use of filtration products.

The integrity testing principle - Establishing correlation to bacterial challenge data

During the design process for a new filter product, filter manufacturers such as GE Heathcare, validate the filtration performance to industry defined standards. The Pharmaceutical Industry specifies a sterilising grade filter as one:

rated at 0.22µm or less, capable of producing a sterile filtrate when challenged with a solution containing sufficient Brevundimonas diminuta organisms to give a concentration of 107 per cm² of effective filtration area (EFA).

This is the only specification that is currently documented in regulatory guidelines, however other filter ratings are assessed similarly using different challenge organisms, for example

- 0.10 µm Acholeplasma laidlawii
- 0.10 µm *Acholeplasma laidlawii*
- 0.45 µm *Serratia marcescens*

Filter materials have inherent variation in pore structure and dependent on the manufacturing process, can be produced at a range of pore sizes by modification of processing parameters. As part of the validation process in the development of a membrane material and subsequently a filter product, a large number of samples are taken from the manufacturing process and subjected to bacterial challenge with the organisms identified above. The process for performing a micro-organism challenge with Brevundimonas diminuta is defined in two documents. HIMA (Health Industry Manufacturers Association) now redefined as AdvaMed (Advanced Medical Technology Association) issued a guidance document No.3 Vol. 4 Microbiological Evaluation of Filters for Sterilizing Liquids in April 1992. ASTM (American Society for Testing and Materials) subsequently issued a standard F838-83 Standard Test Method for Determining Bacterial Retention of Membrane Filters Utilized for Liquid Filtration. Both documents are referenced by the industry, although ASTM F838-83 is the now adopted standard method.

Prior to bacterial challenge each filter is tested using an appropr ate non-destructive Integrity Tests.

The objective of this 'correlation' process is to identify the boundary value, given by the non-destructive test for a filter, below which filters consistently provide a sterile filtrate following bacterial challenge. Once this boundary value for the non-destructive integrity test has been identified, it is usual to apply an additional safety factor in defining the user integrity test limit. GE Heathcare applies a safety factor, such that the recommended value for the integrity test limit is 75% of the highest value at which a sterile filtrate was obtained during the bacterial challenge. The results of these tests are usually displayed in a chart similar to the one shown in figure 1.

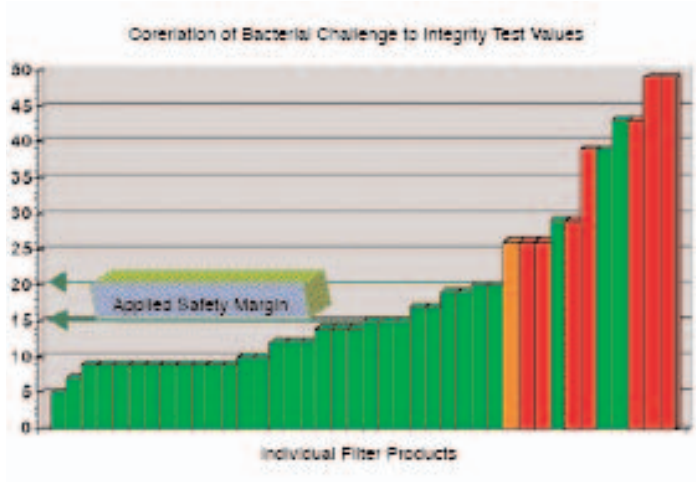


Figure 1. Typical Bacterial Challenge v Integrity Test Value Correlation Chart

In this example, the boundary integrity test value was 20 (notional units), below which all filters tested produced a sterile filtrate. Following the application of an additional safety margin, the user integrity test limit for this product would be set at 15.

The integrity test methods

Currently there are three main identified Integrity Test Methods for Liquid Filters, with two additional methods solely for use with hydrophobic gas filters.

Liquid filter test methods

Bubble Point: the minimum applied differential pressure required to vent the largest pore in a wetted filter media / membrane

Diffusional Flow: the gas flow rate resulting from gas diffusion across a wetted filter media at an applied differential pressure of approximately 80% of the bubble point for that media.

Pressure Decay: the drop in gas pressure measured over time from a sealed volume connected to the upstream side of a wetted filter media due to diffusional flow. This is simply another way of measuring a diffusional flow

Hydrophobic gas filter test methods

Water Intrusion: the volume of water that penetrates (intrudes) into the structure of a hydrophobic media at a given applied pressure held for 10 minutes.

Aerosol Challenge: the concentration of a sub-micron challenge aerosol that penetrates a filter when challenged at a given upstream concentration.

(Note: These methods are not covered in this document. For further details see GE Heathcare support document)

Integrity test principles

Gas flow through a wetted filter media

The basic principle used in most methodologies is the measur ment of a gas flow due to an applied pressure differential through a fully wetted filter media. This principle is usually applied only to membrane based filter products. This is because the pore structure and size distribution is normally sub-micron and the mass flow of gas measured across the membrane through the structure can be accurately measured with enough sensitivity to differentiate between a 'good' and 'bad' structure.

Consider a microporous membrane material wetted thoroughly by a suitable wetting fluid. All the pores are filled with the wetting liquid and held in the pores by surface tension and associated capillary forces.

If a differential pressure is now applied using an applied gas pressure on one side of the wetted membrane, two things can happen:

The gas can dissolve in the liquid in the pores -

The amount of gas that dissolves is dependent on the solubility of the gas in the liquid and also the applied pressure. This phenomenon results in a high concentration of dissolved gas at the pressurised side of the membrane, and a low concentration at the low-pressure side. The gas molecules therefore diffuse across the pore structure to the low-pressure side due to this concentration gradient and come out of solution on the low-pressure side. The resulting transfer of gas is measured as a gas flow is therefore referred to as diffusional flow.

If pressure is increased high enough the wetting liquid can be forced from the larger pores -

The wetting liquid is held in the pores by capillary forces. These forces are built up due to surface interactions between wetting liquids and the polymers that make up the membrane. If sufficient external force is applied, for example, by an applied gas pressure, then the capillary forces can be overcome and the pores can be totally emptied of wetting liquid. At this point the surface of the membrane is seen to bubble, as the escaping gas flows directly through a shallow pool of the liquid on the downstream side, hence the term bubble point. The larger the pore the lower the force required to vent it of liquid. Therefore, theoretically, the first bubble seen indicates the largest pore in the membrane structure.

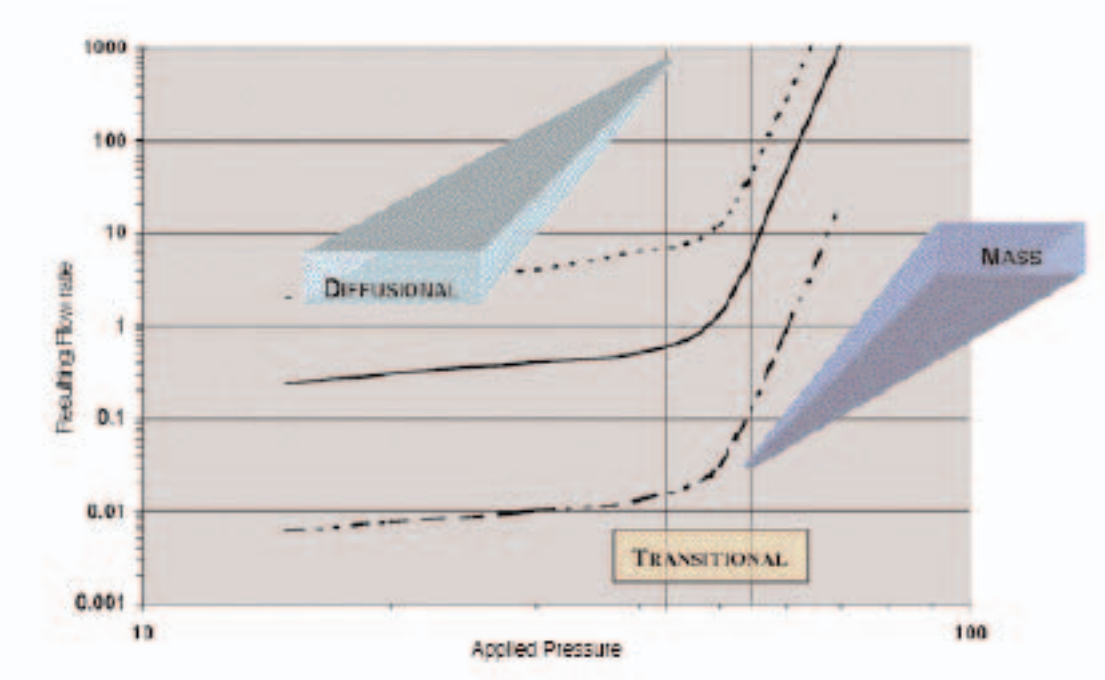


Figure 2. Gas Flow through a Wetted Microporous Filter Media

The flow through a wetted microporous filter media can therefore be summarised by three distinct zones. At low applied differential pressure, the increase in flow rate is almost linear when plotted on log / log axes with applied differential pressure – the Diffusional Flow Zone. As the pressure approaches the 'bubble point', the curve turns non-linear as greater numbers of pores are vented by the applied pressure – the Transitional Flow Zone. Once all of the pores have been vented, the curve returns to virtually a linear form on log / log axes – the Mass Flow Zone.

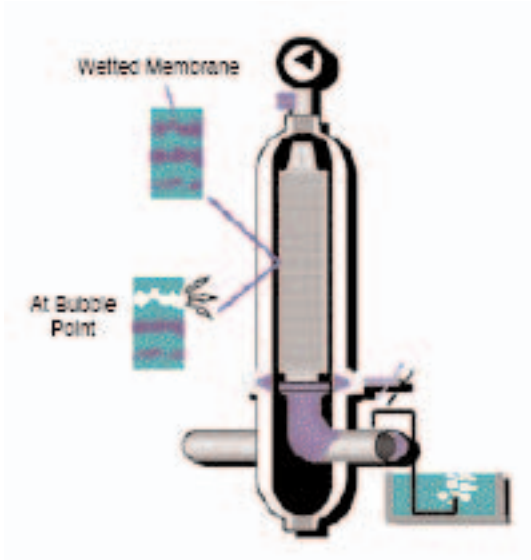
Three simple curves plotted on log / log axes are illustrated in Figure 2 shows the flows for three different areas of media. It will be evident from the curves that the distribution of pore size in the microporous media will determine how short the transitional zone will be. If the distribution is narrow, then all the pores will vent at approximately the same applied pressure and the knee in the curve will be sharp. The wider the distribution, the broader the knee in the curve. The above principles have led to the development of two distinct test methods based on determining either the bubble point or the diffusional flow of gas across the membrane.

The bubble point test

Hydrophilic ("water loving") microporous membranes in contact with water will fill their pores following principles associated with capillary forces. To vacate the filled pores requires a differential pressure to be applied across them.

In a simplified form, the required pressure to vent a liquid filled pore, P, has an inverse relationship to the pore diameter, d, described by the so called bubble point equation:

$$P = \frac{K \times 4 \times \_ \times Cos\_}{d}$$



Where _ is the surface tension of wetting fluid, _ is the contact angle of wetting and K is a pore shape factor constant (since pores are not simple cylinders in real filter membranes).

In any filter media, there is a distribution of many millions of pores. As pressure is increased more pores are vented, the largest ones first. The removal of the wetting liquid from the pores allows a distinct change in the gas flow through the filter media to be measured. It is the applied pressure at which this change in gas flow rate produced that used as the physical indicator or 'bubble point'.

The test is carried out by connecting a compressed air supply to the upstream side of a wetted filter, increasing the applied pressure and then monitoring for a sudden change in gas flow rate.

This procedure can be carried out manually by feeding a pipe connection from the outlet line through an inverted water filled glass vessel and simply looking for a constant stream of air bubbles to be visible.

Issues affecting bubble point testing

Operator subjectivity - What does the bubble point actually measure?

Each operator may have a different protocol that they operate to in terms of how pressure is applied and what constitutes a constant stream of bubbles. Whilst strictly documented and applied protocols can lessen the influence, this can be overcome completely by using automated test equipment.

High pressures required

For sterilising grade filters rated at 0.1µm and higher, the bubble point pressure can be significantly higher than the rated operating pressure of the membrane. The bubble pointing of the product could end in physical damage of the membrane or in the case of capsule product, the product housing and seals.

Different wetting fluids

The surface tension of the wetting fluid will affect the bubble point directly. If a filter has been used to with a specific liquid product, remnants of that product may be difficult to remove from the filter media, or that product may have a direct effect on the surface chemistry of the filter media. If any product fluid still remains in the filter, then once wetted with water this may effect the surface tension. Also, if there changes in surface chemistry in the filter media due to contact with the fluid this may change the wetting angle and hence the bubble point. To overcome these difficulties and avoid the requirement for prolonged flushing protocols, it may be prudent to correlate bubble point values in water for a particular filter to bubble point values in the product fluid to be filtered. The Parenteral Drug Association (PDA) Technical Report No. 26 – Sterilizing Filtration of Liquids published in 1998 gives a protocol to allow this correlation to be produced.

Different filter areas

The size of a filter does not effect the intrinsic bubble point of the material used to construct it. Generally however, a larger area or filter material will give an indicated bubble point lower than expected compared to a smaller area.

The reason for this can be seen if we consider the amount of gas passing through the filter as the media area rises. A 47mm disc presents an area of approximately 10 cm2 and a 10" cartridge perhaps 6000 cm2. As the transition zone (indicated in figure 2) is reached and the flow rate starts to increase, the point at which a change occurs will vary significantly. For the 47mm disc, in the region of 0.02 to 0.10 ml/min, and with the 10" cartridge, 8 - 30 ml/min. Assuming that the device used to detect the differences has a fixed sensitivity for assessing the change in gas flow, be it the human eye or a physical detector, the change in flow rate in the larger filter will always be detected before the smaller. To an observer of the 10-fold air flow increase, it appears much more like a bubble point at a lower pressure with the larger area than with the smaller area. Automated machines do much to alleviate this issue, but it is still a common practice for cartridge bubble points to be quoted as lower than 47mm disc bubble points.

At the other end of the scale, with multi-round filter assemblies for example, the difficulty is maintaining sensitivity at much higher initial flow rates. Consider an 18 round 30" assembly, where even a significant increase in flow rate for one module may be masked by the high overall diffusional flow rate from the other 539 x 10" modules.

Multiple layer filters

Several observers have reported that an increase in thickness of membrane results in an increase in bubble point values. This can result in multi-layer products utilising the same grade of final membrane, having increased bubble points ratings over a single layer of the same material.

Change in temperature

Temperature changes impact on several physical interaction parameters. The surface tension of the wetting fluid or the solubility of the test gas in the fluid may change. In cases where a fixed upstream pressure is applied to the membrane, as for example with pressure decay testing, change in temperature results in a corresponding change in pressure. All these effects can produce significant impacts on the measured bubble point, and therefore maintenance of a stable temperature is a key to accurate - repeatable integrity testing.

Rapid changes in pressure

The procedure to find the bubble point of a particular membrane based filter requires the pressure to be raised. The rate at which the pressure is increased can have a dramatic effect on the measured bubble point. The more rapid the pressure increase the less time the system has to stabilise and due to lags in the diffusional flow equalisation rate and the sampling system if downstream monitoring is used, the more likely it is to measure a false high (good) bubble point. Again, standardised protocols and automated test equipment mitigate against this potential source of error.

Procedure for wetting

Most false low bubble point integrity test failures can be put down to issues associated with achieving full wetting of the pore structure. If the pores of the filter are not completely wetted then a low bubble point will be measured. The recommended procedure to ensure wetting is to allow the filter to stand in the wetting solution, typically water, for 5 minutes and then flow the fluid through the filter at 10 l/min per 10" cartridge for 2 – 3 minutes with an operating pressure of 1 – 2 bar. In cases where the integrity test value is still suspect, as a final check, a flush with an alcohol, typically IPA, or hot water can result in full wetting being achieved. Testing in a wetting solution of 60%: 40% IPA: Water can also be used where wetting difficulties are encountered.

Filter material issues

The higher the hydrophobicity of the membrane and other constructional materials for the filter, the greater the potential for variation in bubble point due to incomplete wetting.

Not all filters of the same ratings will exhibit the same bubble point. This is due to the wetting angle differences with each polymer and liquid combination. Also remember that rating is usually measured against an ability to remove a specified organism from a fluid stream, not necessarily the effective pore size. Hence all 0.2Ìm rated products do not have the same bubble point some observers using terms such as 'tight' and 'open'.

Automated testing algorithm differences

Automated bubble point test equipment supplied by different manufacturers may determine the bubble point using different physical parameter measurement e.g. using measurement of pressure loss or measurement of direct mass flow. Instruments using the same principle may also potentially use different algorithms to calculate the bubble point e.g. the pressure at which the flow rate starts to go non- linear compared to the pressure at which extrapolations of the linear portions of the flow curve intersect. This can result in slight differences in measured bubble point comparing one manufacturer's machine to another and variation depending which method or machine was applied to producing the initial correlation to bacterial challenge data.

Diffusional flow tests

Diffusional flow based tests operate with applied pressures to measure gas flows in the diffusional zone.

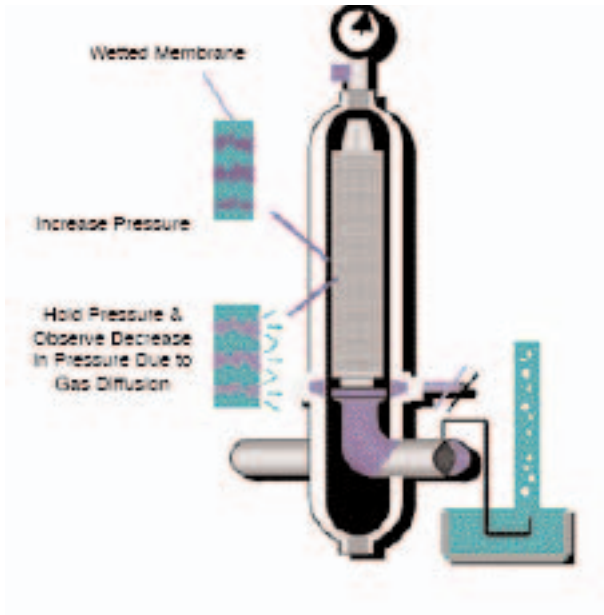
Gas flow in this zone is produced due to pressure dependent gas solubility in the wetting liquid and transportation of the dissolved gas through the wetting liquid due to a concentration gradient.

At the upstream side of a wetted pore, gas dissolves into the surface layer following Henry's law which states that the amount of gas dissolved in a liquid is a function of the partial pressure of the gas above it. As the dissolved gas passes across the pore depth the pressure drops and the gas re-emerges and is released at the downstream surface of the pore in accordance with Henry's Law. The rate of gas diffusion through the liquid follows Fick's Law, remodelled by Reti (1977) that states:

Two different physical measurement methods are currently used:

- *Pressure Decay / Pressure Hold Measurement*
- *Diffusional Flow Measurement by Mass Flow*

$$N = \frac{D \times H \times (p1-p2) \times \_}{L}$$



Where N is the permeation rate (number of moles of gas per unit time), D is the diffusivity of the gas in the liquid, H is the solubility coefficient of the gas, and L is the depth of the liquid, and _ is the void volume of the membrane.

This results in the diffusion rate being directly related to the applied pressure differential and is therefore linear for given values of the other variables.

Pressure decay / Pressure hold

This, the most commonly adopted method, measures the gas pressure loss from a pressurised, sealed upstream volume due to diffusional flow across a membrane filter which is then equated to a gas flow rate. If the vessel volume is known then the pressure drop can be related to the loss in gas by the general gas equation:

$$P \times V = n \times R \times T = (m/M) \times R \times T$$

Gas initially contained in a closed system of known volume V at pressure P is then left for a set time to diffuse out of the system through a wetted filter. The change in pressure P then relates directly to the mass of gas lost through diffusion, and if the time is known the diffusional flow rate can be calculated.

$$\frac{(P_1 - P_2) \times V}{t}$$

Where P_1 is the starting pressure in bar

P_2 is the finish pressure in bar

V is the sealed upstream volume in ml

t is the time in mins

Diffusional flow measurement from pressure decay

Indirect measurement of diffusional flow is achieved by including in the measurement system a method of measuring the upstream volume. This removes the uncertainty of the Pressure Decay method, which relies on an accurate volume being already known. The GE Heathcare PORECHECK 3 incorporates a procedure for physically measuring the upstream volume. This is achieved by first filling a vessel of known volume, (located within the instrument), with compressed air or nitrogen gas and then venting it into the upstream void. The new pressure resulting in the upstream void added to the defined volume can allow the upstream volume to be calculated by the use of Boyle's Law again, P1V1 = P2V2. A pressure decay test can now be run as normal and the loss in pressure related directly back to a volumetric flow of gas, the Diffusional Flow.

Diffusional flow measurement by mass flow

Direct measurement using mass flow transducer technology can eliminate the requirement for knowing the upstream volume of the system being tested. Mass Flow sensors can be used to measure the gas flow directly at a constant maintained pressure differential.

IThis technique is currently only limited to a few particular test instruments and is not yet applied widely.

Issues affecting diffusional flow testing

What does diffusional flow testing actually measure? The diffusional flow test methods assess the effective porosity of a filter membrane. Any flaw in the membrane will be identified due to an increase in diffusional flow. Any change in structure not only associated with the 'largest' pore as measured by the bubble point method will also be identified. As with the bubble point method however, the numbers obtained from a diffusive flow measurement only have significance as they are correlated to a bacterial challenge. The measurement accuracy for diffusive flow can however be improved compared with bubble point assessments as the subjectivity associated with bubble point measurement is removed.

Measurements of high area filters

As shown above, increases in the area of a filter membrane in a product can give problems with the identification of the bubble point, as the impact of the high levels of diffusional flow blur the transition point. Most manufacturers will recommend the use of diffusional flow for larger filter systems.

Requirement to know the upstream volume

The most common method to assess diffusional flow for a membrane filter uses a pressure decay methodology as previously described. This requires the upstream volume to be known accurately. GE Heathcare supplies details of it's own housing volumes when GE Heathcare filter products are being used. In cases where alternative suppliers have supplied the housings, this data may not be readily available. Current integrity test instruments incorporate this measurement capability as part of the testing protocol.

Selection of integrity test

GE Heathcare recommends that the diffusional flow test be applied to most products in capsule and cartridge format. Diffusional flow testing is simple to perform using automated test instruments such as the PORECHECK Integrity Tester, and avoids some difficulties in maintaining repeatability which is associated with the bubble point method.

In cases where the filter media area is small, i.e. discs, there is no real alternative to bubble point testing as the diffusional flow rates are so small that the sensitivity of the automated instruments do not allow their use.

Integrity test methods - Procedures

When to test

The EU cGMP Guidelines resulting from the 2001/83/EC and 2001/82/EC Directives for Human and Veterinary Drug Products state in Annex 1 Manufacture of Sterile Medicinal Products: -

"The integrity of the sterilised filter should be verified before use and should be confirmed immediately after use by an appropriate method such as bubble point, diffusion flow or pressure hold test."

If steaming protocols are in place, then the ideal is to test post initial sterilisation, perhaps in the first product filtered and subsequently immediately post filtration, again in the process fluid. GE Heathcare can provide a service to identify the appropriate integrity test value for process wetting fluids.

The US cGMP guidelines are documented in the Code of Federal Regulations. There are no specifics identified here, however, in the CDER Guidance for Industry (1997) the Guideline on Sterile Drug Products Produced by Aseptic Processing (June 1987) is reviewed where reference is made to integrity testing under section Sterilization Operations, Filtration:

Normally, integrity testing of the filter is performed after the filter unit is assembled and sterilised prior to use. More importantly, however, such testing should be conducted after the filter is used in order to detect any filter leaks or perforations that may have occurred during the filtration. "Forward Flow", "bubble point" and "pressure hold" tests are acceptable integrity tests.

Wetting the filter on test

If the steaming of the filter or other processing issues prevent wetting in process fluids as above, then it may be required to wet the filter with water before integrity testing. This will normally be achieved using the appropriate grade of pharmaceutical water used in the process, often Water for Injection (WFI). To ensure that the products are fully wetted, the GE Heathcare guideline for flushing is:

Cartridges / Capsules:	Flush for 3 minutes at 15 to 20 litres per min per 10" (250mm) module
Discs: 47mm - 10ml	90mm - 50ml
142mm - 100ml	293mm - 500ml

It is very important to ensure that the pore structure for the filter to be tested has been fully wetted. Any trapped gas in the filter or hydrophobic areas will distort the final reading significantly leading to the potential of false fails being registered.

It is important to note that after processing some fluids, the traces of product can be difficult to remove. Often the fluid can introduce some hydrophobicity into the filter products, which results in false fails in integrity testing. Under these circumstances appropriate procedures must be considered such as hot water flushing or flushing with mild compatible solvents. An alternative approach can also be considered using a better wetting solution such as ISO Propyl Alcohol / Water mixes.

Another increasingly common approach is to consider testing in the product itself, with Integrity Test values derived and validated by GE Heathcare Technical Support Group (TSG).

Dip wetting (simply submerging a filter product in liquid) has been used successfully on occasion, but is not a recommended procedure and must be validated by the user into standard operating procedures.

Technical support group activities

GE Heathcare have a trained team of scientists and engineers available to answer questions regarding the technical capabilities of our products, to assist in the selection and design of appropriate filtration systems and to provide user training programs. The following services can be delivered both on site and in-house;

- filterability testing to optimise filter system design
- advice on the development of integrity testing, steam sterilisation and clean in place procedures
- development of validation procedures
- troubleshooting
- facility audits to ensure continued optimisation of filter use
- operator training including filtration theory, filter system design and management, validation, etc.

For more information on any of the above support services please contact your local GE Heathcare representative.

website: www.GEHealthcare.com/filtration

www.gehealthcare.com/filtration

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